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Thermal and non-thermal health effects of low intensity non-ionizing radiation: An international perspective☆

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ABSTRACT

Exposure to low frequency and radiofrequency electromagnetic fields at low intensities poses a significant health hazard that has not been adequately addressed by national and international organizations such as the World Health Organization. There is strong evidence that excessive exposure to mobile phone-frequencies over long periods of time increases the risk of brain cancer both in humans and animals. The mechanism(s) responsible include induction of reactive oxygen species, gene expression alteration and DNA damage through both epigenetic and genetic processes. *In vivo* and *in vitro* studies demonstrate adverse effects on male and female reproduction, almost certainly due to generation of reactive oxygen species. There is increasing evidence the exposures can result in neurobehavioral decrements and that some individuals develop a syndrome of “electro-hypersensitivity” or “microwave illness”, which is one of several syndromes commonly categorized as “idiopathic environmental intolerance”. While the symptoms are non-specific, new biochemical indicators and imaging techniques allow diagnosis that excludes the symptoms as being only psychosomatic. Unfortunately standards set by most national and international bodies are not protective of human health. This is a particular concern in children, given the rapid expansion of use of wireless technologies, the greater susceptibility of the developing nervous system, the hyperconductivity of their brain tissue, the greater penetration of radiofrequency radiation relative to head size and their potential for a longer lifetime exposure.

1. Introduction

Electromagnetic fields (EMFs) are packets of energy that have no mass. They vary in frequency and wavelength. At the high end of the electromagnetic spectrum there are cosmic and X-rays that have enough energy to cause ionization, and therefore are known as ionizing EMFs. Below in frequency and energy are ultraviolet, visible light and infrared EMFs. Excessive exposure to ultraviolet EMFs poses clear danger to human health, but life on earth would not be possible without visible light and infrared EMFs. Below these forms of EMF are those used for communications (radiofrequency or RF-EMFs, 30 kHz-300 GHz) and those generated by electricity (extremely low-frequency or ELF-EMFs, 3 Hz-3 kHz). These EMFs do not have sufficient energy to directly cause ionization, and are therefore known as non-ionizing radiation. RF-EMFs at sufficient intensity cause tissue heating, which is the basis of operation of the microwave oven. However the question to be addressed here is human health effects secondary to exposures to non-ionizing EMFs at low intensities that do not cause measureable heating.

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In spite of a large body of evidence for human health hazards from non-ionizing EMFs at intensities that do not cause measureable tissue heating, summarized in an encyclopedic fashion in the Bioinitiative Report (www.bioinitiative.org), the World Health Organization (WHO) and governmental agencies in many countries have not taken steps to warn of the health hazards resulting from exposures to EMFs at low, non-thermal intensities, nor have they set exposure standards that are adequately health protective. In 2001 the International Agency for Research on Cancer (IARC, 2002), part of the WHO, declared ELF-EMFs to be "possibly carcinogenic to humans", and in 2011 they made a similar declaration for RF-EMFs (Baan et al., 2011; IARC, 2013). The classification of RF-EMFs as a "possible" human carcinogen was based primarily on evidence that long-term users of mobile phones held to the head resulted in an elevated risk of developing brain cancer. One major reason that the rating was not at "probable" or "known" was the lack of clear evidence from animal studies for exposure leading to cancer. The US National Toxicology Program has released preliminary results of a study of long term exposure of rats to cell phone radiation which resulted in a statistically significant increase in brain gliomas, the same cancer found in people after long-term cell phone use, and schwannomas, a tumor similar to the acoustic neuroma also seen after intensive mobile phone use (Wyde et al., 2016). Similar results in rats have been reported in an independent study at the Ramazzini Institute with exposures similar to those from a mobile phone base station (Falcioni et al., 2018). This evidence, in conjunction with the human studies, demonstrates conclusively that excessive exposure to RF-EMF results in an increased risk of cancer. In light of this new evidence for cancer in rodents in response to prolonged exposure to mobile phone frequencies, the IARC rating should be raised at least to "probable" (Group 2A) if not "known" (Group 1).

Unfortunately the International EMF Project of the WHO, which is part of the Department of Public Health, Environment and Social Determinants of Health in Geneva, has consistently minimized health concerns from non-ionizing EMFs at intensities that do not cause tissue heating (WHO, 2014). In this regard WHO has failed to provide an accurate and human health-protective analysis of the dangers posed to health, especially to the health of children, resulting from exposure to non-thermal levels of electromagnetic fields. The Department of Public Health, Environment and Social Determinates of Disease takes its advice on the issues related to human health effects of non-ionizing EMFs from the International Commission on Non-ionizing Radiation Protection (ICNIRP). Almost all members of the core group preparing the new Environmental Health Criteria (EHC) document for the WHO are members of ICNIRP (Starkey, 2016; Hardell, 2017), a non-goverment organization (NGO) whose members are appointed by other members. In spite of recent efforts to control for conflicts of interest, ICNIRP has a long record of close associations with industry (Maisch, 2006). When queried as to why the WHO would take recommendations from such a group, WHO staff replied that ICNIRP is an official NGO which works closely with the WHO. Why this should exclude other scientific research groups and public health professionals is unclear, particularly since most members of ICNIRP are not active researchers in this field. We are particularly concerned that a new WHO EHC document on RF-EMFs is scheduled to be released soon, and that the members of the EHC Core Group and the individuals whose assistance has been acknowledged are known to be in denial of serious non-thermal effects of RF-EMFs in spite of overwhelming scientific evidence to the contrary (Starkey, 2016; Hardell, 2017).

Others have dismissed the strong evidence for harm from ELF- and RF-EMFs by arguing that we do not know the mechanism whereby such low energetic EMFs might cause cancer and other diseases. We have definitive evidence that use of a mobile phone results in changes in brain metabolism (Volkow et al., 2011). We know that low-intensity ELF- and RF-EMFs generate reactive oxygen species (ROS), alter calcium metabolism and change gene expression through epigenetic mechanims, any of which may result in development of cancer and/or other diseases or physiological changes (see www.bioinitiative.org for many references). We do not know the mechanisms behind many known human carcinogens, dioxins and arsenic being two examples. Given the strength of the evidence for harm to humans it is imperative to reduce human exposure to EMFs. This is the essence of the "precautionary principle".

There are a number of reasons for our concern. In the past the major exposure of the general population to RF-EMFs came from radio and television signals. Now there are almost as many mobile phones as there are people in the world, all of them being exposed to RF-EMFs. There are mobile phone towers everywhere, and in many developing countries there are no land-lines that allow communication without exposure to RF-EMFs. There is rapid movement in many developed countries to place small cell transmitting devices (5G) operating at higher frequencies (24–70 GHz) every approximately 300 m along sidewalks in residential neighborhoods. There are other significant sources of exposure, coming from WiFi, smart meters and soon from automobiles operating without a human driver. Therefore human exposure has increased dramatically in recent years, and continues to increase rapidly. While we already are seeing harm from these exposures, the degree of harm will only increase with time because of the latency that is known to occur between exposure and development of diseases such as cancer.

Standards for protection of human health from EMFs vary greatly around the world. Many countries set standards based on the false assumption that there are no adverse health effects of RF-EMFs other than those that are caused by tissue heating. This is the case in North America, Australia and some European countries. Many countries from the former Soviet Union have much more restrictive standards. However information from cellular and human studies show biological effects that constitute hazards to human health at exposure levels that are often exceeded during daily life.

This report follows a recent non-official meeting in Geneva with WHO representives, where the authors urged WHO to acknowlege low intensity effects of ELF-EMFs and non-thermal health effects of RF-EMFs. This report does not attempt to present a complete overview of the subject [see the Bioinitiative Report (www.bioinitiative.org) for that] but rather to provide a holistic picture of the processes explaining most or all of the adverse effects of EMF exposures. It summarizes the evidence for cancer resulting from exposure to EMFs, and identifies other diseases or pathological conditions such as Alzheimer's disease and hypofertility that have been shown to be associated with excesive exposure to low-intensity EMFs. We also focus on electrohypersensitivity (EHS) in both children and adults and cognitive and behavioural problems in children resulting from the increasing exposure. Finally we discuss what is known about the mechanisms whereby non-thermal EMF radiation can cause disease with special reference to EMF-related free radical production and epigenetic and genetic mechanisms.

2. Mobile phone use and the risk for glioma, meningioma and acoustic neuroma

The brain is the main target for exposure to RF-EMF radiation during use of handheld wireless phones, both mobile and cordless phones (Cardis et al., 2008; Gandhi et al., 2012). An increased risk for brain tumors has been of concern for a long time. The results of the Swedish National Inpatient Register have documented an

increasing incidence of brain tumors in recent years (Carlberg and Hardell, 2017). In May 2011 RF radiation in the frequency range 30 kHz–300 GHz was evaluated to be a Group 2B, i.e. a "possible" human carcinogen, by IARC (Baan et al., 2011; IARC, 2013). This was based on an increased risk for glioma and acoustic neuroma in human epidemiological studies. In the following an updated summary is given of case-control studies on brain and head tumors; glioma, meningioma and acoustic neuroma. The Danish cohort study on 'mobile phone users' (Johansen et al., 2001; Schüz et al., 2006) is not included due to serious methodological shortcomings in the study design, including misclassification of exposure (see Söderqvist et al., 2012a).

2.1. Glioma

Glioma is the most common malignant brain tumor and represents about 60% of all central nervous system (CNS) tumors. Most of these are astrocytic tumors that can be divided into low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). The most common glioma type is glioblastoma multiforme (WHO grade IV) with peak incidence in the age group 45–75 years and median survival less than one year (Ohgaki and Kleihues, 2005). Three research groups have provided results in case-control studies on glioma (Interphone, 2010; Coureau et al., 2014; Hardell and Carlberg, 2015). Hardell and colleagues have published results from case-control studies on use of wireless phones and brain tumor risk since the end of the 1990s (Hardell et al., 1990; for more discussion see Carlberg and Hardell, 2017).

A random effects model was used for meta-analyses of published studies, based on test for heterogeneity in the overall group ("all mobile"). Note that only the Hardell group also assessed use of cordless phones. Thus their reference category included cases and controls with no use of wireless phones in contrast to the other studies investigating only mobile phone use. In Table 1 results for highest cumulative use in hours of mobile phones is given. All studies reported statistically significant increased risk for glioma and the meta-analysis yielded an odds ratio (OR) = 1.90 [95% confidence interval (CI) = 1.31–2.76]. For ipsilateral mobile phone use the risk increased further to OR = 2.54 (95% CI = 1.83–3.52) in the meta-analysis based on 247 exposed cases and 202 controls.

Carlberg and Hardell (2014) found shorter survival in patients with glioblastoma multiforme associated with use of wireless phones compared with patients with no use. Interestingly mutation of the p53 gene involved in disease progression has been reported in glioblastoma multiforme in patients with mobile phone use ≥3 h per day. The mutation was statistically significantly correlated with shorter overall survival time (Akhavan-Sigari et al., 2014). Further support for the increased risk of glioma associated with mobile phone use has been obtained in additional analyses of parts of the Interphone study (Cardis et al., 2011; Grell et al., 2016; Momoli et al., 2017).

2.2. Meningioma

Meningioma is an encapsulated, well-demarked and rarely malignant tumor. It is the most common benign tumor and accounts for about 30% of intracranial neoplasms. It develops from the pia and arachnoid membranes that cover the CNS. It is slowly growing and gives neurological symptoms by compression of adjacent structures. The most common symptoms are headaches and seizures. The incidence is about two times higher in women than in men. Meningioma develops mostly among middle aged and older persons (Cea-Soriano et al., 2012). Carlberg and Hardell (2015) included meningioma in their case-control studies. The results of the meta-analysis for cumulative exposure in the highest category are given in Table 2. In total there was an increased (but not statistically significant) risk for cumulative exposure but the increased risk was statistically significant for ipsilateral use of mobile phones (OR = 1.49, 95% CI = 1.08–2.06).

2.3. Acoustic neuroma

Acoustic neuroma, also called vestibular schwannoma, is a benign tumor located on the eighth cranial nerve from the inner ear to the brain. It is usually encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It grows slowly and due to the narrow anatomical space may give compression of vital brain stem structures. First symptoms of acoustic neuroma are usually tinnitus and hearing problems. Results for use of mobile phones in Interphone (2011) and Hardell et al. (2013) are given in Table 3. Statistically significant increased risk was found for cumulative ipsilateral use ≥1640 h yielding OR = 2.71 (95% CI = 1.72–4.28).

The study by Moon et al. (2014) was not included in the meta-analysis because data on cumulative mobile phone use with numbers of cases and controls were not given. Support of an increased risk was seen in the case-case part of the study (Moon et al., 2014) and also in the report by Sato et al. (2011). Pettersson et al. (2014) made a case-control study on acoustic neuroma in Sweden not overlapping the Hardell et al. (2013) study. An increased risk for the highest category of cumulative use of both mobile phone (≥680 h OR = 1.46, 95% CI = 0.98–2.17) and cordless phone (≥900 h OR = 1.67, 95% CI = 1.13–2.49) was found. Pettersson et al. (2014) was not included in the meta-analysis due to the many scientific shortcomings in the study, e.g. laterality analysis was not made for cordless phone, the numbers in the laterality analysis for mobile phone are not consistent in text and tables and the 'unexposed' reference category included subjects using either mobile and cordless phone, which is clearly not correct (Hardell and Carlberg, 2014).

Table 1
Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95% confidence interval (CI) for glioma in case-control studies in the highest category of cumulative hours of mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone 2010						
Cumulative use ≥1640 h	210/154	1.40	1.03–1.89	100/62	1.96	1.22–3.16
Coureau et al., 2014						
Cumulative use ≥896 h	24/22	2.89	1.41–5.93	9/7	2.11	0.73–6.08
Carlberg and Hardell, 2015						
Cumulative use ≥1640 h	211/301	2.13	1.61–2.82	138/133	3.11	2.18–4.44
Meta-analysis						
Longest cumulative use	445/477	1.90	1.31–2.76	247/202	2.54	1.83–3.52

Table 2
Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95% confidence interval (CI) for meningioma in case-control studies in the highest category of cumulative hours of mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone 2010						
Cumulative use ≥1640 h	130/107	1.15	0.81–1.62	46/35	1.45	0.80–2.61
Coureau et al., 2014						
Cumulative use ≥896 h	13/9	2.57	1.02–6.44	6/4	2.29	0.58–8.97
Carlberg and Hardell 2015						
Cumulative use ≥1640 h	141/301	1.24	0.93–1.66	67/133	1.46	0.98–2.17
Meta-analysis						
Longest cumulative use	284/417	1.27	0.98–1.66	119/172	1.49	1.08–2.06

Table 3
Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95% confidence interval (CI) for acoustic neuroma in case-control studies in the highest category of cumulative hours of mobile phone use.

	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone 2011						
Cumulative use ≥1640 h	77/107	1.32	0.88–1.97	47/46	2.33	1.23–4.40
Hardell et al., 2013						
Cumulative use ≥1640 h	27/301	2.40	1.39–4.16	19/133	3.18	1.65–6.12
Meta-analysis						
Cumulative use ≥1640 h	104/408	1.73	0.96–3.09	66/179	2.71	1.72–4.28

2.4. *In summary*

Based on case-control studies there was a consistent finding of increased risk for glioma and acoustic neuroma associated with use of mobile phones. Similar results were found for cordless phones in the Hardell group studies, although such use was not reported by the other study groups. The findings are less consistent for meningioma although somewhat increased risk was seen in the meta-analysis of ipsilateral mobile phone use. A longer follow-up time is necessary for this type of slow growing tumor.

The results on glioma and acoustic neuroma are supported by results from animal studies showing co-carcinogenic and tumor promoting effects from RF-EMF (Tillmann et al., 2010; Lerchl et al., 2015). Recent results from the National Toxicology Program (NTP) study showed genotoxicity of RF radiation in rats and mice exposed to RF-EMF (Smith-Roe et al., 2017). That result supports previous findings of DNA strand breaks in rat brain cells exposed to RF-EMF (Lai and Singh, 1997).

Of importance also is that the results in the NTP and Ramazzini studies both demonstrated an increased incidence of tumors of the same type, glioma and malignant schwannoma, as has been seen in humans with mobile phone use (Wyde et al., 2016; Falcioni et al., 2018). Acoustic neuroma (vestibular schwannoma) is a similar type of tumor as malignant schwannoma, although benign. In fact, rates of brain tumors are increasing in Sweden and use of wireless phones has been suggested to be the cause (Hardell and Carlberg. 2017).

3. Other diseases and pathological conditions attributed to exposure to low-intensity EMFs

The evidence for harm from RF-EMF is strongest for cancer as a consequence of intensive mobile phone use, especially gliomas, glioblastomas and acoustic neuromas. But there is other evidence for elevation in risk of leukemia among children living near to very high intensity radio transmission towers (Michelozzi et al., 2002; Ha et al., 2007). This is particularly interesting because leukemia is the cancer most associated with elevated exposure to ELF-EMFs arising from power lines (Ahlbom et al., 2000; Greenland et al., 2000). There is some evidence for elevations in breast cancer risk among women who wear their mobile phones in their bra (West et al., 2013). Heavy use of a mobile phone was associated with significantly elevated rates of ipsilateral parotid tumors in studies from both Israel (Sadetzki et al., 2007) and China (Duan et al., 2011). No increased risk was found in a Swedish study, but the results were limited by low number of participants and lack of data on heavy and long-term use of wireless phones (Söderqvist et al., 2012b).

There are other significant human health hazards of concern. There is strong animal and human evidence that exposure to RF-EMFs as well as ELF-EMFs reduces fertility in both males (reviewed by McGill and Agarwal, 2014) and females (Roshangar et al., 2014). An association between spontaneous abortion and non-thermal EMF exposure including ELF-EMFs was reported in several case-control studies (Dodge, 1970; Juutilainen et al., 1993; Li et al., 2017). The increased use of mobile phones and increased exposure coming from WiFi, smart meters and other wireless devices has been paralled in time with male hypofertility and sperm abnormalities in semen (Rolland et al., 2013). These effects may be related to holding an active wireless laptop in a man's lap or having an active mobile phone on their belt, but more study is needed. There is evidence that isolated human sperm exposed to RF-EMFs are damaged by generation of reactive oxygen species (Agarwal et al., 2009).

There are other diseases or physiologic alterations which have been reported to be associated with exposure to non-thermal EMFs in humans and in animals (Belyaev et al., 2016). Alzheimer disease has been shown to be significantly associated with chronic ELF-EMF occupational exposure in prospective epidemiological studies (García et al., 2008; Davanipour and Sobel, 2009). Exposure to RF-EMFs has been reported to increase neuropsychiatric and behavioural disorders (Johansson et al., 2010; Divan et al., 2012), trigger cardiac rhythm alteration and peripheral arterial pressure instability (Havas, 2013; Saili et al., 2015), induce changes in immune system function (Lyle et al., 1983; Grigoriev et al., 2010; Sannino et al., 2011, 2014) and alter salivary (Augner et al., 2010) and

thyroid (Koyu et al., 2005; Mortavazi et al., 2009; Pawlak et al., 2014) function. There is an urgent need for more study of these diseases or biological alterations in relation to exposure to both ELF- and RF-EMFs.

4. An emerging concern: cognitive and neurobehavioral problems in children

Children, and especially fetuses, are more vulnerable than adults for most environmental exposures (Sly and Carpenter, 2012). This is because their cells are rapidly dividing and their organ systems are not mature. As a result, events that perturb cellular function early in life can result is abnormalities that last. There is a building body of evidence indicating that exposure to RF-EMFs has adverse effects on cognition and neurobehavior, especially in children and adolescents. Concern about the particular sensitivity of children to RF-EMFs emitted from mobile phone was first raised in 2000 by a British independent expert group (IEG, 2000) that noted that the increased sensitivity to EMFs of children could be due not only to the natural vulnerability of the developing nervous system, but also to the smaller head size and thickness of the skull. These factors, plus the higher conductivity of the young nervous system, result in greater penetration of RF-EMFs into the brain (Gandhi et al., 1996). Of concern is the fact that any adverse effects during development may have life-long consequences and that young people, because they will have a longer life span, will receive a greater cumulative exposure than adults (Kheifets et al., 2005; Hansson Mild et al., 2006).

There are several reasons to be concerned. Animal studies have shown that *in utero* RF-EMF exposure from mobile phones affects fetal programming and leads to alteration in neurodevelopment and behavior of offsprings (Aldad et al., 2012; Zhang et al., 2015). Exposure of young rats to non-thermal intensities impairs learning and spatial memory secondary to a deleterious impact of EMFs on hippocampal, pyramidal or cortical neurons. Similar detrimental cognitive and behavioural defects were also observed in adult animals exposed to low-intensity.

EMFs (Bas et al., 2009; Deshmukh et al., 2015; Kumari et al., 2017; Shahin et al., 2017). The exposure induces markers of oxidative stress and inflammation in the brain (Dasdag et al., 2012; Megha et al., 2015).

There are human data consistent with these animal studies. Divan et al. (2008) reported that prenatal and to a lesser degree postnatal exposure to cell phones is associated with emotional and hyperactivity problems in 7-year old children. This finding was confirmed in a second replicative study involving different participants (Divan et al., 2012). Birks et al. (2017) used data from studies in five cohorts from five different countries (83,884 children) and concluded that maternal mobile phone use during pregnancy increased the risk that the child will show hyperactivity and inattention problems. A meta-analysis involving 125,198 children (mean age 14.5 years) reported statistically significant associations between access to and use of portable screen-based media devices (e.g. mobile phones and tablets) and inadequate sleep quality and quantity and excessive daytime sleepiness (Carter et al., 2016). Early life exposure to lead has long been known to cause a reduction in cognitive function and shortened attention span (Needleman et al., 1979). Two studies have shown that prenatal (Choi et al., 2017) or postnatal (Byun et al., 2017) mobile phone exposure results in greater neurobehavioral effects in children with elevated lead levels than those seen with elevated lead alone. These results raise concern that EMFs may have synergistic actions with other environmental contaminants known to cause a reduction in intelligence quotient (IQ) and attention, such as polychlorinated biphenyls, methyl mercury, environmental tobacco smoke and probably others (Carpenter, 2006).

Finally the problem should be considered at the societal, worldwide level. Many adolescents (Lenhart, 2015) and even very young children and infants (Kabali et al., 2015) use cordless devices immoderately, to such a point that the common intensive use of devices in children and adolescents has been ascribed as an addiction (Paz de la Puente and Balmori, 2007; Roberts et al., 2014).

The specific absorption rate (SAR)-based ICNIRP safety limits were established on the basis of simulation of EMF energy absorption using standardized adult male phantoms, and designed to protect people only from the thermal effects of EMFs. These assumptions are not valid for two reasons. Not only do they fail to consider the specific morphological and bioclinical vulnerabilities of children, but also they ignore the effects known to occur at non-thermal intensities. The same criticisms apply to other so called “independent” advisory groups or agencies, such as the Advisory Group of Non-Ionizing Radiation in the UK (AGNIR, 2012), the French Agency for Food, Environmental and Occupational Health & Safety in France (ANSES, 2013), and the Scientific Committee on Emerging Newly Identified Health Risk (SCENIHR, 2009), all of whom deny the detrimental health effects of low intensity, non thermal EMF exposure and make recommendations based only on thermal SAR considerations.

Although several scientific authorities, such as the US American Academy of Pediatrics (AAP, 2013), and the Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP, 2011) have made specific recommendations to not allow the use of mobile phones by children and to limit their use by adolescents, unfortunately these age categories remain a target for marketing of mobile phone devices [http://www.who.int/peh-emf/project/mapnatreps/RUSSIA%20report%202008.pdf]. The RNCNIRP has warned that if no rational, health-based safety limits are adopted for children and adolescents and no measures are taken to limit the use of cordless devices, we can expect disruption of memory, decreases in learning and cognitive capabilities, increases in irritability, sleep disturbance, and loss of stress adaptation in this population. There will also be long-term effects, including an increase in brain cancer, infertility, EHS, Alzheimer disease and other neurodegenerative diseases (RNCNIRP, 2011; Markov and Grigoriev, 2015). National and international bodies, particularly the WHO, will bear major responsiblity for failing to provide specific science-based guidance and recommendations so as to avoid such global health threats.

5. Electrohypersensitivity, microwave illness or idiopathic environmental intolerance attributed to electromagnetic fields

There is a segment of the human population that is unusually intolerant to EMFs. The term “electromagnetic hypersensitivity” or “electrohypersensitivity (EHS)” to describe the clinical conditions in these patients was first used in a report prepared by a European group of experts for the European Commission (Bergqvist et al., 1997). Santini et al. (2001, 2003) reported similar symptoms occurring in users of digital cellular phones and among people living near mobile phone base stations.

In 2004, because of the seemingly increasing worldwide prevalence, WHO organized an international scientific workshop in Prague in order to define and characterize EHS. Although not acknowledging EHS as being caused by EMF exposure, the Prague working group report clearly defined EHS as “a phenomenon where individuals experience adverse health effects while using or being in the vicinity of devices emanating electric, magnetic or electromagnetic fields” (www.who.int/pehemf/EHS_Proceedings_June2006.pdf). Following this meeting, WHO acknowledged EHS as an adverse health condition (WHO, 2005).

According to the Prague Workshop recommendations, it was proposed to use the term "idiopathic environmental intolerance (IEI) attributed to electromagnetic fields" (IEI-EMF) because of the lack of a proven causal link with EMF exposure (Hansson Mild et al., 2006). This pathological disorder is identical to what has been previously described under the term "microwave illness" (Carpenter, 2015).

This syndrome is characterized by fatigue, chronic pain and impaired cognitive function (see the Paris appeal, http://appel-de-paris.com/?lang=en). The precise mechanism(s) whereby environmental exposure to either ELF- or RF-EMFs can cause the development of this syndrome are still uncertain. However several lines of experimental and clinical data are sufficiently strong so as to indicate that ELF-EMFs and RF-EMFs exposure is associated with adverse biological and clinical health effects in humans as well as animals (Rea et al., 1991; McCarty et al., 2011; Belpomme et al., 2015; Hedendahl et al., 2015; Irigaray et al., 2018a). The prevalence of EHS has been estimated to range 1–10% in developed countries (Hallberg and Oberfeld, 2006) but appears today to be around 3% (Huang et al., 2018).

Since WHO official reports on mobile phone exposure and public health (WHO, 2014) and more particularly on EHS (WHO, 2005), much clinical and biological progress has been made to identify and objectively characterize EHS, as was summarized during the international scientific consensus meeting of the 5th Paris Appeal Congress that took place in May 2015 in Brussels at the Royal Belgium Academy of Medicine (ISD, 2015). EHS has many characteristics in common with other IEI pathological disorders, including chronic fatigue syndrome, fibromyalgia, Gulf War Illness and especially the syndrome of multiple chemical senssitvity (MCS), which Belpomme et al. (2015) have shown to be associated with EHS in many patients who report being electrohypersensitive.

5.1. Bioclinical identification and characterisation of electrohypersensitivity

In a prospective study involving systematic face-to-face questionnaire-based interviews and clinical physical examinations of nearly two thousand patients who self-reported having EHS or EHS and MCS, Belpomme and colleagues reported that EHS is a well-defined clinico-biological entity, characterized by the progressive occurrence of neurologic symptoms, including headache, tinnitus, hyperacusis, superficial and/or deep sensibility abnormalities, fibromyalgia, vegetative nerve dysfunction and reduced cognitive capability. These symptoms are repeatedly reported by the patients to occur each time they are exposed to EMFs, even of weak intensity. They result in chronic insomnia, fatigue, emotional lability and depressive tendency (Belpomme et al., 2015; Irigaray et al., 2018b).

Table 4 presents the detailed symptomatic picture which was obtained during face-to-face interviews with subjects with EHS in comparison to those with both EHS and MCS and to a series of apparently healthy control subjects that showed no evidence of EHS and/or MCS. As shown in the Table, the symptoms reported are consistent with those in other published questionnaire-based studies of EHS patients (Dodge, 1970; Johansson et al., 2010; Nordin et al., 2014; Medeiros and Sanchez, 2016; Röösli, 2008). The clinical symptoms observed in EHS or EHS/MCS patients are statistically significantly much more frequent that those in apparently normal controls. Although many of these symptoms are non-specific, the general clinical picture resulting from their association and frequency strongly suggests that EHS can be recognized and identified as a specific neurological disorder.

Because of the multiple and relatively common symptoms and the lack of recognized objective diagnosis criteria, studies on EHS were left with only the patient's self-reported interpretation for many years. As a result, EHS has unfortunately been considered to be a psychiatric disease of unknown origin. This helps explain why most mainstream public health and societal bodies claim there is not sufficient data proving that the clinical symptoms experienced and reported by EHS patients are caused by EMF exposure. Therefore they refuse to acknowledge EHS as a true neuropathological disorder. This negative point of view was supported by some blind or double blind studies showing that most individuals who report they suffer from EHS were not able to identify when they were exposed to either EMFs or sham controls (Rubin et al., 2011; Eltiti et al., 2015). However other studies have found that EHS subjects can identify EMF exposure in a statistically significant manner when they are blinded to whether or not the exposure was on (Rea et al., 1991; McCarty et al., 2011).

To account for these seemingly negative results a nocebo effect was suggested (ANSES, 2017). However there is presently no consensus on a biological mechanism through which a nocebo effect could occur (Medeiros and Sanchez, 2016; Chrousos and Gold, 1992; Jakovljevic, 2014). Moreover, results obtained in a carefully designed psycho-clinical study in self-reporting EHS patients are not consistent with an initial nocebo response to perceived EMF exposure, even though it is plausible that after the onset of the disease such phenomena may intervene secondarily through an acquired learning and conditioning process (Dieudonné, 2016). In addition, a meta-analysis of cross sectional studies has documented a 38% greater risk of development of headaches among mobile phone users than non-users, and an increasing risk of headache with longer daily call duration (Wang et al., 2017).

Belpomme, Irigaray and colleagues recently identified several biomarkers in EHS and/or MCS patients which allow physicians to identify and objectively characterize EHS as a true somatic pathological disorder, discounting the hypothesis of a causal psychosomatic or nocebo-related process. These came in part from a prospective clinical and biological analysis of a series of several hundred consecutive cases of individuals who self-reported that they suffered from EHS or both EHS and MCS (Belpomme et al., 2015) and more recently from the prospective anlaysis of an additional series of EHS patients (Irigaray et al., 2018a). Table 5 summarizes the different biomarkers that have been measured in the peripheral blood of these patients and the results which have been obtained based on the EHS and EHS/MCS patient groups. Note that among the different markers, the 6-hydroxymelatonin sulfate/creatinine ratio in urine appears to be the best marker to be used in medical practice since it has been found to be decreased in all cases evaluated to date (Belpomme et al., 2015).

By measuring different major oxidative stress-related biomarkers, such as thiobarbituric acid reactive substances (TBARS), oxided glutathione (GSSG) and nitrotyrosine (NTT) in EHS patients, Irigaray et al. (2018b) have recently shown that near 80% of the EHS patients present with detectable oxidative stress biomarkers (Fig. 1). More than 40% of EHS patients present with at least one positive biomarker, 20% with two and 15% will all three of the biomarkers investigated. This indicates that in addition to the inflammation-related biomarkers previously associated with EHS, EHS patients are also characterized by exhibiting biomarkers of oxidative stress (Belpomme et al., 2015; Irigaray et al., 2018a,b).

The significance of the different biomarkers measured in the peripheral blood of EHS and EHS/MCS patients is that these results imply that these patients present with some degree of oxidative/nitrosative stress, inflammation and autoimmune response. Increased levels of several of these markers (notably protein S100B and NTT) may reflect hypoxia-associated oxidative stress-induced blood brain barrier (BBB) opening. It has been previously hypothesized that opening of the BBB can be caused by environmental

Table 4
Clinical symptom occurrence in EHS and EHS/MCS patients in comparaison with normal controls[a].

	EHS	EHS/MCS	p[b]	Normal controls	p[c]	p[d]
Headache	88%	96%	0.065	0%	<0.0001	<0.0001
Dysesthesia	82%	96%	0.002	0%	<0.0001	<0.0001
Myalgia	48%	76%	<0.0001	6%	<0.0001	<0.0001
Arthralgia	30%	56%	<0.001	18%	0.067	<0.0001
Ear heat/otalgia	70%	90%	<0.001	0%	<0.0001	<0.0001
Tinnitus	60%	88%	<0.0001	6%	<0.0001	<0.0001
Hyperacousis	40%	52%	0.118	6%	<0.0001	<0.0001
Dizziness	70%	68%	0.878	0%	<0.0001	<0.0001
Balance disorder	42%	52%	0.202	0%	<0.0001	<0.0001
Concentration/Attention deficiency	76%	88%	0.041	0%	<0.0001	<0.0001
Loss of immediate memory	70%	84%	0.028	6%	<0.0001	<0.0001
Confusion	8%	20%	0.023	0%	0.007	<0.0001
Fatigue	88%	94%	0.216	12%	<0.0001	<0.0001
Insomnia	74%	92%	0.001	6%	<0.0001	<0.0001
Depression tendency	60%	76%	0.022	0%	<0.0001	<0.0001
Suicidal ideation	20%	40%	0.003	0%	<0.0001	<0.0001
Transitory cardiovascular abnormalities	50%	56%	0.479	0%	<0.0001	<0.0001
Occular deficiency	48%	56%	0.322	0%	<0.0001	<0.0001
Anxiety/Panic	38%	28%	0.176	0%	<0.0001	<0.0001
Emotivity	20%	20%	1	12%	0.176	0.176
Irritability	24%	24%	1	6%	<0.001	<0.001
Skin lesions	16%	45%	<0.0001	0%	<0.0001	<0.0001
Global body dysthermia	14%	8%	0.258	0%	<0.0001	<0.007

[a] This data results from the clinical analysis of the 100 first clinically evaluated cases issued from the already published series of EHS and/or MCS patients who have been investigated for biological markers [Belpomme et al., 2015]. It has been compared symptomatically with data obtained from a series of 50 apparently normal subjects matched for age and sex, used as controls.
[b] Significance levels (p values) obtained for compararison between the EHS and EHS/MCS groups.
[c] Significance levels (p values) obtained for compararison between the EHS and normal control groups.
[d] Significance levels (p values) obtained for compararison between the EHS/MCS and normal control groups.

Table 5
Patient mean values and standard deviations of biomarker levels in comparison with normal reference values as well as the percentage of patients with abnormal values in the peripheral blood in subjects with EHS or both EHS and MCS (Belpomme et al., 2015).

Biomarker and Normal reference values	Patients groups			
	EHS Mean ± SD	% Above normal	EHS/MCS Mean ± SD	% Above Normal[a]
hs-CRP < 3 mg/l	10.3 ± 1.9	15%	6.9 +/1.7	14.3%
Vitamine D > 30 ng/ml	20.6 ± 0.5	69.3%	14.5 ± 1.3	70.1%
Histamine< 10 nmol/l	13.6 ± 0.2	37%	13.6 ± 0.4	41.5%
IgE< 100 UI/ml	329.5 ± 43.9	22%	385 ± 70	24.7%
S100B < 0.105 µg/l	0.20 ± 0.03	14.7%	0.17 ± 0.03	19.7%
Hsp 70 < 5 ng/ml	8.2 ± 0.2	18.7%	8 ± 0.3	25.4%
Hsp 27< 5 ng/ml	7.3 ± 0.2	25.8%	7.2 ± 0.3	31.8%
Anti-O-myelin auto-antibodies[b]	Positive	22.9%	Positive	23.6%
24-h urine 6-OHMS/creatinine ratio >0.8[c]	0.042 ± 0.003	100%	0.048 ± 0.006	100%

hs-CRP, high-sensitivity C-reactive protein; IgE, Immunoglobulin E; S100B, S 100 calcium binding protein B; Hsp 27, heat shock protein 27; Hsp 70, heat shock protein 70; anti-O-myelin auto-antibodies, auto-antibodies against O-myelin; 6-OHMS, 6-hydroxymelatonin sulfate.
[a] There is no statistically significant difference between the two groups of patients for the different biomarkers analyzed, suggesting that EHS and MCS share a common pathological mechanism for genesis.
[b] Qualitative test.
[c] Data restricted to those not on neuroleptic medication as the simultaneous use of several psychotherapeutic drugs may also be associated with a decrease of this 24-h urine ratio by modifying melatonine metabolism.

stressors, be they chemicals or EMFs. This may have occurred in these patients, as has been shown to occur in several (but not all) animal experiments involving EMF exposure (Oscar and Hawkins, 1977; Persson et al., 1997; Eberhardt et al., 2008; Sirav and Seyhan, 2009). Comparable data using metabolic and genetic biomarkers were also obtained in another large series of EHS patients (De Luca et al., 2014). Overall these data indicate that the clinical use of biomarkers allows the objective characterisation and identification of EHS and MCS as two etiopathologic facets of a unique pathological disorder, and also allows insight into the genesis of these two diseases.

The development of new imaging techniques has also greatly increased our ability to objectively characterize EHS and MCS. Using ultrasonic cerebral tomosphygmography (UCTS) (Parini et al., 1984), EHS- and EHS/MCS-patients were found to have a statistically significant decrease in mean pulsometric index in several middle cerebral artery-dependant portions of the temporal lobes, especially in the capsulo-thalamic area, which is part of the limbic

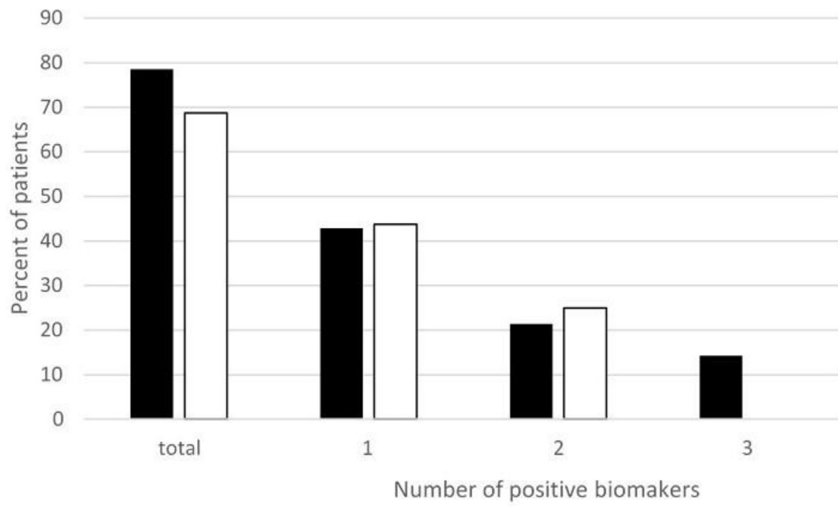

Fig. 1. Percentage of EHS self-reporting patients having positive TBARs, GSSG and/or NTT oxidative stress biomarkers measured in the peripheral blood. "Positive" biomarkers correspond to marker levels above the upper normal limit; "total" corresponds to the patients with one or more positive biomarker levels. Black bars show the percentage of patients with one, two or all three of the biomarkers for TBARS, GSSG and NTT. The white bars show the percentage of patients with either TBARs or GSSG or both oxidative stress markers.

system and the thalamus. This suggests that EHS and EHS/MCS may be associated with a brain blood flow (BBF) deficiency and/or neuronal dysfunction in these brain structures (Belpomme et al., 2015; Irigaray et al., 2018a,b). Irigaray et al. (2018c) have recently confirmed that UCTS is the best imaging technique to diagnose EHS and to follow patients treated for EHS and/or MCS.

In addition, using positron emission tomography (PET) it has been shown that short term exposure to pulse-modulated RF-EMF causally affects regional BBF in normal subjects using a mobile phone (Aalto et al., 2006; Huber et al., 2005), a finding that may account for the modifications observed in the sleep and waking EEG (Huber et al., 2002). By use of functional MRI (fMRI) in EHS patients exposed chronically to ELF-EMFs, regional BBF changes have been reported in the frontal lobes, such as abnormal default mode network and more particularly a decrease in BBF and cerebral metabolism. These observations indicate that fMRI may also be a tool for diagnosis of EHS and clinical follow up of patients (Heuser and Heuser, 2017). A decreased BBF-associated pulsometric index decrease in both hemispheres was also recently observed by the Belpomme group by using transcranial Doppler ultrasound (TDU) (Purlauastja and Sorond, 2012) applied to the middle cerebral artery in a study involving 120 EHS and/or MCS patients. This study revealed a decrease in pulsatility index and an increase in diastolic flow velocity in 70% of the 120 cases investigated to date.

In summary it is the strong opinion of the authors that there is presently sufficient clinical, biological and radiological data emanating from different independent international scientific research groups for EHS, whatever its causal origin, to be acknowledged as a well-defined, objectively characterized pathological disorder. As a result, patients who self-report that they suffer from EHS should be diagnosed and treated utilizing presently available objective biological tests, among which are the concentration of peripheral blood biomarkers and the use of imaging techniques such as PET, fMRI and TDU and, when available, UCTS. Whatever its etiological origin and mechanism of action, EHS should be acknowledge by the WHO as a real and distinct neurological and pathological disorder (McCarty et al., 2011; Hedendahl et al., 2015) and thus be included in the International Classification of Diseases.

5.2. Possible etiopathogenic processes involved in genesis of electro-hypersensitivity

EMFs, both RF-EMFs at non-thermal intensities and ELF-EMFs, have been found to cause persistent adverse biological effects in microorganisms (Fojt et al., 2004), plants (Roux et al., 2008; Maffei, 2014), birds (Balmori, 2005; Balmori and Hallberg, 2007; Frey, 1993), and mammals. Therefore the effects observed in humans cannot be due to only a nocebo or psychosomatic effect. These biological effects may be due both to the pulsed and polarised characteristics of man-made EMFs emitted by electric or wireless technologies as opposed to the terrestrial non-polarised and continuously emitted natural EMFs (Blackman, 2009; Belyaev, 2015; Panagopoulos et al., 2015).

The inflammatory and oxidative/nitrosative states that have been documented in EHS patients are remarkable since they confirm the data obtained experimentally in animals exposed to non-thermal EMFs (Esmekaya et al., 2011; Burlaka et al., 2013), and especially in the brain (Megha et al., 2015; Kesari et al., 2011). The limbic system—associated capsulo-thalamic abnormalities that the Belpomme group has observed by using UCTS in EHS and/or MCS patients (Belpomme et al., 2015; Irigaray et al., 2018a,c) may likely correspond to the hippocampal neuronal alterations caused by EMF exposure in the rats (Bas et al., 2009; Furtado-Filho et al., 2015; Deshmukh et al., 2013). Fig. 2 summarizes our hypothesis regarding the inflammation and oxidative stress-related mechanisms which may account for EMF- and/or chemically-related health effects in the brain and consequently for EHS genesis.

6. Mechanisms whereby low intensity electromagnetic fields cause biological effects and harm

Arguments used in the past to attempt to discount the evidence showing deleterious health effects of ELF-EMFs and RF-EMF exposure at non-thermal SAR levels were based on the difficulties encountered in understanding the underlying biological effects and the lack of recognized basic molecular mechanisms accounting for these effects. This is no longer the case. There are a number of well-documented effects of low intensity EMFs that are the mechanistic basis behind the biological effects documented above (www.

bioinitiative.org). These include induction of oxidative stress, DNA damage, epigenetic changes, altered gene expression and induction including inhibition of DNA repair and changes in intracelluar calcium metabolism. Both low-intensity ELF-EMF and non-thermal RF-EMF effects depend on a number of physical parameters and biological variables and physical parameters, which account for the variation in health outcomes (Belyaev, 2015; Belyaev et al., 1999). Importantly, the most severe health effects are observed with prolonged chronic exposures even when intensities are very low (Belyaev, 2017). The physics of non-equilibrium and non-linear systems and quantum mechanics are at least in part the basis of the physical mechanisms responsible for the non-thermal molecular and biological effects of non-thermal EMF radiation (Belyaev, 2015), although a detailed report on these actions is beyond the scope of this review.

Lower RF-EMF intensity is not necessarily less bioactive or less harmful. Non-thermal EMF effects can be observed at intensities which are very close to ordinary background levels and quite similar to intensities emitted by mobile phone base stations. There are time windows for observation of non-thermal EMF effects which may be dependent upon the endpoint measured, the cell type and the duration and power density of exposure. Non-thermal RF-EMF effects are affected by static magnetic fields and electromagnetic stray fields, which result in the variation of non-thermal EMF effects from mobile phones because of adjacent electrical appliances, power lines and other sources of ELF and static magnetic fields, including changes in the geomagnetic field (Gapeev et al., 1999a and b).

Cell-to-cell interactions potentiate the response to non-thermal EMFs (Belyaev et al., 1996). Biological responses to EMFs have been shown to be influenced by sex and age (Zhang et al., 2015; Sirav and Seyhan, 2016). Physiological parameters such as the stage of cell growth, oxygen, divalent ions and temperature are important variables affecting cellular responses to EMFs (Liburdy and Vanek, 1987; Sannino et al., 2011).

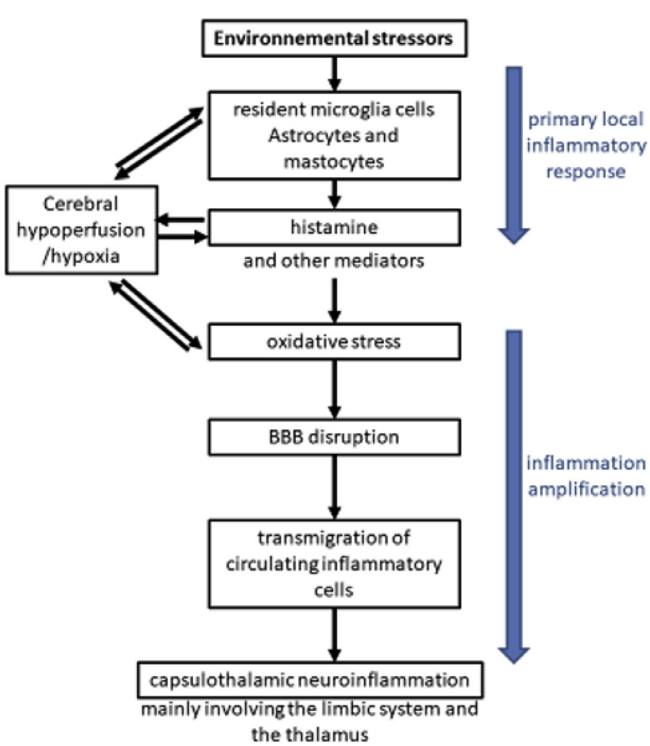

Fig. 2. Hypothetical EHS/MCS common etiopathogenic model based on neuro-inflammation and oxidative/nitrosative stress-induced blood brain barrier disruption (Belpomme et al., 2015).

6.1. Combined exposures

EMFs at non-thermal intensities may interfere with other environmental stressors, showing an interplay of molecular pathways and resulting in either beneficial or detrimental health effects, depending on the nature and conditions of co-exposures (Novoselova et al., 2017; Ji et al., 2016). One example is the demonstration that RF-EMF exposure modulates the DNA damage and repair induced by ionizing radiation (Belyaev et al., 1993). Another example is the synergistic of exposure to lead and EMFs on cognitive function in children described above (Choi et al., 2017; Byun et al., 2017). These co-exposure factors should be considered when assessment of detrimental effects, including carcinogenicity, is performed.

Not all of the effects of EMFs on the nervous system and other organs are necessarily harmful. The best example of a positive effect is the well-documented and clinically useful benefit of applied magnetic fields to promote bone healing (Bassett, 1994). Both ELF-EMF (Zhang et al., 2015) and RF-EMF (Arendash et al., 2010) have been reported to slow cognitive decline in rodent models of Alzheimer's disease. Some human studies report a facilitating effects of cognitive performance (Lee et al., 2001) while Koivisto et al. (2000) reported an increase in response time and vigilance tasks but a decrease in mental arithmetric tasks. These studies clearly show that EMFs have biological effects at non-thermal intensities, but suggest that not all biological effects are necessarily harmful.

6.2. Duration of exposure and dose intensity

Such parameters as power density, dose, and duration of exposure have been analyzed for development of reliable safety standards, which would protect against the detrimental health effects of chronic exposure to RF-EMFs at non-thermal intensities. Some studies show no effect under fixed short-term exposures, but this does not imply that there are no effects from longer-term exposures (Choi et al., 2014). Exposure in studies showing RF-EMF effects was on average twice the duration as those with no significant effects (Cucurachi et al., 2013). The response to non-thermal EMFs depends on both power density and duration of exposure. Importantly, the same response is observed with lower power density but prolonged exposure as at higher power density and shorter exposure (Nordenson et al., 1994). While SAR is a good surrogate for thermal RF effects from acute exposures, many studies have shown that SAR should be either replaced by “dose-specific absorption” or power density complimented by duration of exposure for description of non-thermal RF effects (Belyaev, 2015). Recent studies have provided more evidence for the greater importance of dose and duration of exposure than SAR alone for biological and health effects from long-term exposures to non-thermal RF-EMFs (Furtado-Filho et al., 2015).

6.3. Oxidative stress

Non-ionizing radiation does not have sufficient energy to directly break chemical bonds, and therefore the DNA damage that occurs with non-ionizing EMF exposures is primarily a consequence of generation of reactive oxygen species (ROS), resulting in oxidative stress. There are numerous animal experiments which clearly demonstrate that non thermal EMFs can cause oxidative stress (Esmekaya et al., 2011; Burlaka et al., 2013), particularly in the brain (Shahin et al., 2017; Dasdag et al., 2012; Megha et al., 2015; Furtado-Filho et al., 2015). Oxidative stress is known to

play a central role in development of cancer and aging and serves as a signaling agent in the inflammatory response (Holmstrom and Finkel, 2014).

The brain is a particularly important organ for sensitivity to EMFs. Brain cancer resulting from EMF exposures is a serious concern, and EHS is a disease of the central nervous system. Several mechanisms at the cellular and molecular levels have been reported that may be the basis of these non-thermal RF-EMF effects on brain function. ELF- and/or RF-EMF exposure at embryonic or early postnatal stages can alter *in vivo* synaptic efficacy and plasticity of neurons (Balassa et al., 2014), a finding which was further supported by *in vitro* studies showing a significant decrease in the differentiation of neural stem cells into neurons (Eghlidospour et al., 2017), the alteration of transcript levels of neuronal differentiation-related genes and impairment of neurite outgrowth of embryonic neural stem cells exposed to ELF- or RF-EMFs (Ma et al., 2014). These observations support the conclusion that low-intensity but prolonged exposure to non-thermal EMFs may have adverse effects on neurogenesis during development and indicate how important it is to protect the fetus and young child from excessive exposure to all mobile devices.

Animal studies have documented that 900 MHz or 2.45 GHz non thermal RF-EMF exposure in rats, either short term or chronic, can trigger neuronal dysfunction and even apoptosis of hippocampal pyramidal cells (Bas et al., 2009; Shahin et al., 2017) and cerebellum Purkinje cells (Sonmez et al., 2010) through induction of oxidative stress. Exposure of pregnant dams elicited EMF oxidative stress-induced neuronal pathologic changes in offspring (Odaci et al., 2016). Such pathological changes could be due to ROS-induced opening of the BBB (Nordal and Wong, 2005) and/or to ROS-associated brain hypoxia caused by a decrease in EMF-induced BBF and/or EMF-induced hemoglobin deoxygenation (Mousavy et al., 2009; Muehsam et al., 2013). The resulting hypoxia may induce metabolic neuronal dysfunction as in the case of EHS patients (Belpomme et al., 2015) but also neuronal cell death by either apoptosis or necrosis as in the case of Alzheimer's disease and other forms of dementia (Bell and Zlokovic, 2009).

While some consider the laboratory data on EMFs as being inconsistent, showing either detrimental or no effects and on occasion even beneficial effects, the vast majority still show detrimental effects. For example Henry Lai in the Bioinitiative Report Research Summaries Update of November 2017, Chapter 6 on Genotoxic Effects, reported that i) of 46 studies on ELF genotoxicity with the comet assay as the end point, 34 studies (74%) showed detrimental effects, ii). Of 189 total studies on ELF and oxidative stress, 162 (87%) showed a positive correlation, and iii) of 200 studies on RF and free radicals, 180 (90%) showed detrimental effects. One reason for variability between laboratory studies is the strong dependence on low-threshold EMF effects on a number of physical and biological variables (Belyaev, 2010).

6.4. Genetic and epigenetic mechanisms

Genetic effects are the most direct cause for carcinogenicity. This is true both for genotoxic changes caused by exposure to EMFs and existing polymorphic genetic differences within a population that increase susceptibility to cancer. DNA can no longer be considered to be unaffected by environmental EMF levels, as many studies have shown that DNA can be activated and damaged by EMFs at levels that have been considered to be safe (Blank and Goodman, 1999).

The primary mechanism through which low-intensity EMFs can alter DNA is through ROS production. Lai and Singh (2004) first reported that a 2 h exposure of rats to 60 Hz EMFs at 0.1–0.5 mT resulted in DNA strand breaks in neurons, and provided evidence that this effect was mediated by free radical formation and blocked by free radical scavengers. Vijayalaxmi and Prihoda (2009) in a meta-analysis of 87 publications found a biologically small but statistically significant difference between DNA damage in ELF-EMF-exposed somatic cells as compared to controls, and reported evidence for epigenetic changes for some outcomes. For ELF-EMFs this breakage effect was stronger when exposure was intermittent rather than continuous (Nordenson et al., 1994).

Yang et al. (2008) have reported an OR = 4.31 (95% CI = 1.54–12.08) for leukemia in children living within 100 m of a high voltage powerline if they had a certain polymorphism of a DNA repair gene.

Exposure to RF-EMFs can also induce DNA damage under specific conditions (Markova et al., 2005). Tice et al. (2002) and Vijayalaxmi et al. (2013) reported DNA damage and micronuclei formation in cultured human leukocytes and lymphocytes upon exposure to RF-EMF signals of at least 5 W/kg. Not all cell types showed similar responses. Schwartz et al. (2008) reported micronucleus changes in fibroblasts but not lymphocytes exposed to 1950 MHz EMFs. Kesari et al. (2014) also demonstrated DNA strand breaks in the brains of rats exposed for 2 h per day for 60 days to a 3G mobile phone. Changes in DNA secondary structure (Semin, 1995; Diem et al., 2005) and chromosome instability (Mashevich, 2003) have been observed upon exposure to RF-EMFs emitted by mobile phones.

Epigenetic changes, rather than genetic changes in DNA, may underlie many or even most of the biological effects of non-thermal EMFs (Sage and Burgio, 2017). Non-thermal EMFs are epigenetic stressors which can alter gene expression by acting through physical or biochemical processes and be reflected as chromatin remodeling (Belyaev et al., 1997), histone modification (Wei et al., 1990) or altered microRNA (Dasdag et al., 2015) at intensities far below those that cause measureable tissue heating.

Chromatin plays a key regulatory role in controlling gene expression and, more particularly, the access of transcription factors to DNA. It has been shown that extremely low intensity RF-EMF exposure, i.e. at intensities comparable to that of mobile phone and towers, results in changes in chromatin conformation and gene expression (Belyaev et al., 1997; Belyaev and Kravchenko, 1994; Belyaev et al., 2006; Belyaev et al., 2009). In a large number of cells and tissues, compaction of chromatin in specific loci may lead to gene silencing, loss of histone regulatory effects and DNA repair capacity (Wei et al., 1990). Belyaev and collaborators (Markova et al., 2005; Belyaev et al., 2009) have shown that exposure to RF-EMFs emitted by GSM mobile phone alters chromatin conformation in human lymphocytes and inhibits formation of p53-binding protein 1 (53BP1) and phosphorylated histone H2AX (γ-H2AX) DNA repair foci.

EMFs in both the ELF and RF ranges may epigenetically affect DNA by inducing the expression of stress response genes and consequently the synthesis of chaperone stress proteins (Blank and Goodman, 2011a and b). A specific gene sequence has been identified that acts as a sort of antenna, specifically sensitive and responsive to EMFs (Blank and Goodman, 2011b). This is a gene sequence coding for HSP70, a protein belonging to a family of conserved, ubiquitously expressed "heat shock proteins" that sense danger signals and protect cells from the most disparate stress conditions. This is an unambiguous demonstration that EMF exposure even at non-tissue heating intensities has the potential to be harmful to cells and organisms. The HSP70 promotor contains different DNA regions that are specifically sensitive to diverse stressors, thermal and non-thermal. The EMFs are specifically perceived by the sequences sensitive to non-thermal stimuli. During the process of HSP70-response induction, EMFs can activate directly the HSP70 gene promoter (Rodrequez-De la Fuente et al.,

2010) which contains a magnetic field-responsive domain (Lin et al., 1999, 2001).

EMF-related HSP70 and HSP27 stress responses have been detected in the hippocampus of rats exposed to non-thermal EMFs (Yang et al., 2012). Shahin et al. (2017) reported that mice exposed to 2G mobile phones continuously for four months showed elevated ROS, lipid peroxidation, total nitrate and nitrite concentrations and malondialdehyde levels in homogenates of different tissues, and decreased levels of several antioxidant enzymes. These observations justify the use of these markers to characterize EHS in patients who report that they are sensitive to EMFs.

The EMF effects have been suggested to be mediated by the mitogen-activated protein kinase (MAPk) cascades, which is a central signaling transduction pathway which governs all stress-related cellular processes occurring in response to extracellular stimuli (Friedman et al., 2007). It has been shown that long term exposure of cells to mobile phone frequencies or to ELF-EMFs (Goodman et al., 2009) activates the extracellular-signal regulated kinase (ERK), which is one of the four MAPk cascades so far identified.

Non-thermal RF-EMFs may also alter expression of other genes. As long ago as Byus et al., 1988 showed that 450 MHz RF increased ornithine decarboxylase activity in hepatoma cells. Markova et al. (2005) exposed human fibroblasts and mesenchymal stem cells to mobile phone RF-EMFs with analysis of tumor suppressor p53 binding protein 1. Formation of 53BP1 foci was inhibited in both cells types, but the stem cells always showed a greater response. Fragopoulou et al. (2011) exposed mice to either a typical mobile phone or a wireless DECT base station and analyzed the brain proteome. They found significant alteration in 143 specific proteins (ranging from a 0.003 fold downregulation to up to a 114-fold overexpression.) Luo et al. (2013) exposed pregnant women undergoing a first trimester abortion to a mobile phone applied to the abdomen and performed a proteomic analysist of placental villous tissue. They report 15 proteins which were significantly altered by at least 2- to 2.5-fold in exposed women as compared to control women. Twelve of these proteins were identified. Yan et al. (2008) exposed rats to mobile phones 6 h per day for 126 days, and found upregulation of specific mRNAs that regulated several proteins, including calcium ATPase, neural cell adhesion molecule, neural growth factor and vascular endothelial growth factor. EMFs at non thermal levels may not only alter the expression of many proteins but also may directly affect protein conformation (Fragopoulou et al., 2011; Bohr and Bohr, 2013; Beyer et al., 2013) and modify enzyme activity (Vojisavljevic et al., 2010), so altering the regulating capacity of the epigenome. These are epigenetic, not genetic, effects (Sage and Burgio, 2017).

Non-thermal EMF exposure can epigenetically interfere with the differentiation and proliferation programs of stem cells in fetal and adult tissues through ROS production (Wolf et al., 2007; Falone et al., 2007; Ayşe et al., 2010; Park et al., 2014). Stem cells are the most sensitive cells to EMF exposure (Eghlidospour et al., 2017; Markova et al., 2010) and this is particularly the case for neural stem cells of the hippocampus (Leone et al., 2014).

The endogenous natural ionic currents and electrical fields in the human body (Jaffe and Nuccitelli, 1977) are vulnerable to the oscillary properties of non-thermal EMFs. These consequently may cause detrimental effect on cell differentiation and proliferation in adult tissues (Levin, 2003) in addition to the effects on cell differentiation, proliferation and migration in the fetus (Wolf et al., 2007; Ayşe et al., 2010; Leone et al., 2014). Fetal programming cannot be reduced to only genetic programs. Developmental processes are essentially epigenetic (Leone et al., 2014), and exposure to epigenetic stressors such as non-thermal EMFs are much more dangerous for the fetus than for the adults.

6.5. Calcium regulation

There has long been evidence that EMFs alter several aspects of calcium function. This is important because calcium regulates many different aspects of cell function. Bawin and Adey (1976) reported that very weak ELF-EMFs trigger efflux of calcium from isolated chick brain, although the implications of this observation were not clear. Later they reported a similar action of RF-EMFs (Adey et al., 1982). Pulsed low-frequency EMFs promote bone healing and promote calcium uptake into bone (Spadaro and Bergstrom, 2002) and osteoblasts (Zhang et al., 2010). 50 Hz EMFs increase the number of voltage-gated calcium channels in neuroendocrine cells (Grasso et al., 2004) and presynaptic nerve cell terminals (Sun et al., 2016). Wei et al. (2015) found that ELF-EMFs also altered the frequency of calcium transients in cardiomyocytes and decreased calcium concentrations in sarcoplasmic reticulum. These changes in calcium in heart muscle may be the basis for the cardiovascular effects reported in humans on exposure to EMFs (Havas, 2013). In spite of numerous studies reporting altered calcium metabolism upon exposure to both ELF- and RF-EMFs, the overall implications of these effects are still not clear. However, some have suggested (Ledoigt and Belpomme, 2013) that calcium activation of proteins could be the initial event that results in altered protein configuration, leading to generation of ROS and ultimately activating the molecular pathways to cancer.

7. Public Health Implications of Human Exposure to EMFs

The incidence of brain cancer in children and adolescents has increased between 2000 and 2010 (Ostrom et al., 2015). Gliomas are increasing in the Netherlands (Ho et al., 2014), glioblastomas are increasing in Australia (Dobes et al., 2011) and England (Philips et al., 2018) and all brain cancers are increasing in Spain (Etxeberrua et al., 2015) and Sweden (Hardell and Carlberg, 2017). The latency period between initial exposure and clinical occurrence of brain cancer is not known but is estimated to be long. While not all reports of brain cancer rates show an increase, some do. The continually increasing exposure to EMFs from all sources may contribute to these increases. The prevalence of EHS is unknown, but various reports suggest that it is between 1 and 10% of the population (Hallberg and Oberfeld, 2006; Huang et al., 2018). Male fertility has been declining (Geoffroy-Siraudin et al., 2012; Levine et al., 2017). EMFs increase the risk of each of these diseases and others. Alzheimer's disease is increasing in many countries worldwide and its association with ELF-EMF occupational exposure has been clearly demonstrated through several independent epidemiological studies (Davanipour and Sobel, 2009; Sobel et al., 1996; Qiu et al., 2004) and a meta-analysis of these studies (García et al., 2008). A recent meta-analysis (Huss et al., 2018) has reported an increased risk of amyotrophic lateral sclerosis in workers occupationally exposure to ELF-EMFs.

Safety limits for RF exposure have been based (until today) on the thermal effects of EMFs. But these standards do not protect people, particularly children, from the deleterious health effects of non-thermal EMFs (Nazıroğlu et al., 2013; Mahmoudabadi et al., 2015). Each of these diseases is associated with decrements in health and quality of life. Brain cancer patients often die is spite of some improvement in treatment, while EHS patients present with increased levels of distress, inability to work, and progressive social withdrawal. The ability for humans to reproduce is fundamental for the maintenance of our species.

The scientific evidence for harm from EMFs is increasingly strong. We do not advocate going back to the age before electricity or wireless communication, but we deplore the present failure of public health international bodies to recognize the scientific data

showing the adverse effects of EMFs on human health. It is encouraging that some governments are taking action. France has removed WiFi from pre-schools and ordered Wi-Fi to be shut off in elementary schools when not in use (http://www.telegraph.co.uk.news/2017/12/11/france-ipose-total-ban-mobile-phones-schools/). The State of California Department of Public Health has issued a warning on use of mobile phones and offered advice on how to reduce exposure (State of California, 2017). There are many steps that are neither difficult nor expensive that can be taken to use modern technology but in a manner that significally reduces threats to human health.

It is urgent that national and international bodies, particularly the WHO, take this significant public health hazard seriously and make appropriate recommendations for protective measures to reduce exposures. This is especially urgently needed for children and adolescents. It is also important that all parts of society, especially the medical community, educators, and the general public, become informed about the hazards associated with exposure to EMFs and of the steps that can be easily taken to reduce exposure and risk of associated disease.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envpol.2018.07.019.

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David O. Carpenter*

The microwave syndrome or electro-hypersensitivity: historical background

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Abstract: Microwave generating equipment first became common during World War 2 with the development of radar. Soviet bloc countries reported that individuals exposed to microwaves frequently developed headaches, fatigue, loss of appetite, sleepiness, difficulty in concentration, poor memory, emotional instability, and labile cardiovascular function, and established stringent exposure standards. For a variety of reasons these reports were discounted in Western countries, where the prevailing belief was that there could be no adverse health effects of electromagnetic fields (EMFs) that were not mediated by tissue heating. The reported Soviet effects were at lower intensities than those that cause heating. However, there were several accidental exposures of radar operators in Western countries that resulted in persistent symptoms similar to those described above. The Soviets irradiated the US Embassy in Moscow with microwaves during the period 1953–1975, and while no convincing evidence of elevated cancer rates was reported, there were reports of "microwave illness". Officials passed these complaints off as being due to anxiety, not effects of the microwave exposure. There is increasing evidence that the "microwave syndrome" or "electro-hypersensitivity" (EHS) is a real disease that is caused by exposure to EMFs, especially those in the microwave range. The reported incidence of the syndrome is increasing along with increasing exposure to EMFs from electricity, WiFi, mobile phones and towers, smart meters and many other wireless devices. Why some individuals are more sensitive is unclear. While most individuals who report having EHS do not have a specific history of an acute exposure, excessive exposure to EMFs, even for a brief period of time, can induce the syndrome.

Keywords: cognitive dysfunction; electromagnetic fields; headache; insomnia.

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Introduction

Electro-hypersensitivity (EHS) is a syndrome that may include some or all of the following: excessive fatigue, headache, tinnitus, insomnia, photophobia, a feeling of cognitive dysfunction and impaired memory, irritability, pain at various sites and often cardiovascular abnormalities (1). However, these are all relatively common complaints. All of us have on occasion suffered from headaches and insomnia. Because the symptoms are relatively non-specific, and because the adverse health effects of electromagnetic fields (EMFs) is a contentious issue, and also because primary care physicians have no objective diagnostic algorithms by which to diagnose EHS, patients suffering from EHS are often referred to a psychiatrist. There is, however, a body of evidence, both old and more recent, that indicates that these symptoms are triggered by exposure to EMFs in sensitive individuals. This is the case for exposure to both the extra low electromagnetic fields (ELF) coming from electricity and the radiofrequency (RF) EMFs coming from radar, communication devices, WiFi, smart meters and many other forms of wireless devices.

The symptoms of EHS have a number of commonalities to those of several other syndromes, including chronic fatigue, fibromyalgia, multiple chemical sensitivity, Gulf War Illness and others. These are sometimes collectively identified as "idiopathic environmental intolerance". They have in common symptoms of fatigue, weakness, headaches, difficulty concentrating, multiple aches and pains, difficulty with sleep, and often difficulties with balance and vertigo. While the triggering events vary for each of these syndromes, many people suffer from more than one. A critical question is why some develop these sensitivities while others do not.

There are conflicting estimates on what percent of the population suffers from EHS, with some suggesting that between 5 and 10% of people have the syndrome, and that the incidence is increasing with time (2). However, there are several reports of tests of individuals taken into a laboratory and their responses recorded when they were unaware of whether or not an EMF field was being applied. Some of these studies have not shown that individuals who report that they are electro-sensitive are in

fact able to discern if the EMFs are present or not (3–6). However, these reports are balanced by others that show that at least some individuals do respond with adverse symptoms when exposed to EMFs in a blinded fashion (7, 8). Thus not everyone who believes they are electrosensitive really is, but it is also likely that some have the symptoms of EHS but have not identified the cause. Thus the true incidence of EHS is currently not known.

Table 1 lists the symptoms reported in two studies by individuals who believe that they suffer from EHS. These are self-reported symptoms, and because all occur commonly in the general population they illustrate the difficulty in confirming that the cause is exposure to EMFs.

Microwave sickness

Soviet and Eastern European standards for exposure to EMFs have long been much more stringent than those in Western countries (11). As shown in Table 2 the Soviet countries' standard for maximal permissible exposure during the workday is 1,000 times lower than that in the US. These lower standards were set based on concern for the "asthenic syndrome", characterized by fatigue, pain, depression, blood pressure lability, fainting, and "apathic ambulic" disorders consisting of hypersomnia, hypokinesis, hypothalamo-pituitary-suprarenal weakness, and inhibition of sexual and digestive reflexes [reviewed by references (12) and (13)]. Memory and general mental function was also described as being impaired. Frey (14) has reviewed other studies by Soviet scientists who report a variety of behavioral and nervous system affects in animals and humans with EMF exposures much below the levels that cause tissue heating.

Table 1: Reported symptoms from Röösli et al. (9) and Lamech (10).

	Röösli et al. (n=429)	Lamech (n=92)
Insomnia	58%	48%
Headaches	41%	45%
Fatigue	18%	32%
Concentration difficulties	16%	30%
Nervousness	19%	13%

Table 2: US Armed Forces and Soviet standards for maximum permissible exposure to microwaves (10 mW/cm^2=0.01 mW/m^2) [Data from reference (15)].

USDOD standard	USSR standard
10 mW/cm^2	0.01 mW/cm^2 over an entire workday No more than 0.1 mW/cm^2 for more than 2 h No more than 1.0 mW/cm^2 for more than 15–20 min

The strength of the evidence supporting the lower standards in Soviet and Eastern European countries is difficult to evaluate because most publications lack sufficient experimental details regarding exposure parameters and documentation of experimental results. None-the-less these symptoms are very much those that comprise the syndrome of EHS.

During the period 1953–1975 the Soviets irradiated the US Embassy in Moscow with microwaves (2.5–4.0 GHz) at intensities up to 18 µW/cm^2 (16, 17). A health study of 1,800 employees who worked at the Moscow embassy and more than 3,000 dependents was performed by AM Lillienfeld from the Johns Hopkins University, as compared to employees at other embassies in Eastern Europe. The study was never published although he summarized some of the results briefly in a review article (18). The study was reported to not show an excess risk of cancer or early death, but did find significantly more depression, irritability, difficulty in concentrating and more memory loss among the exposed Embassy staff, especially in men. While the intensity of symptoms did not correlate well with the intensity of exposure (19), this could reflect differences in individual susceptibility. However, as emphasized by Johnson-Liakouris (20), the health conditions that were reported match those of the microwave sickness syndrome.

Serious questions (21) have been raised about how the results were reported and interpreted. Goldsmith examined the original report as compared to the information that was released by the US State Department, and found that the conclusions of Prof. Lillienfeld had been altered and in some cases deleted, and found that this was at the request of his contracting officer. Goldsmith concluded that there had been a persistent cover-up and deliberate distortions of the conclusions made by the author of the report. Among other findings he concluded that there was an elevated rate of leukemia among the highly exposed group, and that information on some of the cancers was withheld from Dr. Lillienfeld until after the report was submitted. In a later publication Goldsmith (22) reported that there were more lymphocyte chromosomal changes in the Moscow workers as well. Unfortunately we will probably never know the actual results of this study.

This is, however, other evidence that EHS is a real disease. Djordjevic et al. (23) investigated the health status of 322 radar workers all of whom had 5–10 years of occupational exposure to microwave fields. They did not find

significant differences in clinical or laboratory findings, but did report that the radar operators had more subjective complaints than a control group. This was particularly true for headache, fatigue, irritability, sleep disturbances and inhibition of sexual activity. However, the authors concluded that the subjective complaints likely reflected factors other than microwave exposure, however.

Some of the strongest evidence that EHS is a real syndrome comes from cases of acute high intensity exposure to microwaves of healthy people, which resulted in prolonged illness. Williams and Webb (24) reported effects of two airmen exposed to high levels of RF radiation. After an immediate sensation of heat, they later developed nausea, lightheadedness and extreme apprehension with poor appetite and photosensitivity. Forman et al. (25) reported on two men who were accidentally and acutely exposed to microwave radiation. Both exhibited symptoms of headaches, insomnia, irritability and emotional lability even after a 12-month follow-up. Both also developed hypertension several months after exposure. Schilling (26) reported on three men accidentally exposed to 785 MHz RF radiation. All experienced immediate sensations of heating, followed by pain, headache, numbness and parasthesiae, malaise, diarrhea and skin erythema. The first man, age 44, experienced lassitude, lack of stamina, drowsiness and chronic headache. The symptoms gradually improved over 3 years follow-up, but he still had chronic headaches at 3 years. The second man, age 47, also had lassitude, lack of stamina, drowsiness and chronic left sided frontoparietal headache, which was made worse by exposure to sun or heating. The symptoms improved somewhat over 3 years follow-up but the headaches remained. The third man had a lower exposure and his symptoms almost disappeared after 18 months. Schilling (27) reported on six antenna engineers exposed in two separate incidents. All experienced acute headache, parathesias, diarrhea, malaise and lassitude. Four of the men showed no improvement in symptoms after follow-up for 3 or 4 years, with headache, loss of stamina, several malaise and lassitude being the major symptoms.

Reeves (28) reported on 34 US Air Force personnel who were at some point exposed to RF at intensities greater than the permissible exposure limits. Acute symptoms included a sensation of heat, headaches, muscle pain and photophobia. An unspecified number of these subjects exhibited longer lasting symptoms, but these were dismissed as being due to factors other than the exposure. Two-thirds of the subjects were given psychometric testing and found to have "abnormalities including anti-social personality, mild organic brain syndrome, anxiety, tendency toward hypochondriasis and somatization, and in one case, frank malingering in an individual described as being 'emotionally invested in maintaining symptoms for the purpose of meeting emotional needs'". The author concluded that the several subjects who complained of prolonged fatigue, generalized weakness, irritability, decrease memory and concentration and weight changes "seem to reflect a personal 'coping style' of long duration or else manifestation of pre-exposure organic dysfunction, rather than an acute change attributable to RFR overexposure." This general attitude of dismissal of prolonged symptoms in young, otherwise healthy males is indicative of the general response to EHS. Is seems very unlikely that 2/3rd of young, otherwise healthy US Air Force personnel suffer from serious psychiatric disease!

Does some acute exposure trigger EHS? Case studies

The author has also had opportunity to review the exposure and medical history of several individuals whose history is similar to that of the radar operators. Brief summaries of their exposures and symptoms are given below.

JG was a technical expert at repair of RF generating equipment who prior to an accidental RF exposure was healthy. In 2011 he was called to a site to troubleshoot three radios and antenna cables in a facility where all other RF generation equipment was supposed to be shut down. After 1–2 h of work within the facility he began to feel hot and developed a headache, dizziness and nausea. He left the room and was taken a hospital, where he was found to have mild burns on his face, head and neck. It was subsequently determined that not all of the equipment had been turned off and that he had been exposed to concentrated RF for the whole period of time he was in the room. When seen by a neurologist 1 month later he was found to suffer from headaches, dizziness, photosensitivity, nausea, confusion and difficulty with cognition. His gait was unsteady and he was easily disoriented. He noted that he was more irritable, less spontaneous, had decreased sex drive and memory problems. When he and the author met two and a half years after the exposure he complained of constant headaches, confusion and memory loss, lower back, hip and stomach pain, nausea, weight loss, vertigo and constant anxiety and depression. Thus an acute excessive exposure to RF radiation led to a syndrome of adverse health effects that continued essentially unabated for at least two and a half years, and had all of the characteristics of EHS.

JJ is a 41-year-old man who also was healthy prior to a near electrocution event while working at home. Upon contacting a live wire he froze, lost consciousness for about 30 s, but did not suffer from cardiac problems. He went to the hospital with a very bad headache, but was not found to have other abnormalities. Subsequently he was fatigued, had severe photophobia and very severe headaches, which he had never had before. Four year later he has constant dizziness, frequent headaches, vertigo, and nausea, and the symptoms are greatly increased when he is in the presence of EMFs, particularly RF. Again it appears that an acute exposure caused an increased sensitivity to EMFs which has not gone away over a period of several years. However, in this case the acute exposure was to electric current from the household electricity, including extremely lower frequency EMFs.

DL served multiple tours in the US Army in Afghanistan and Iraq as a gunner in a vehicle that used equipment to detect cell phone-detonated improvised explosive devices (IEDs). These electronic counter measures (ECMs) are vehicle-mounted high-power microwave systems that put out a wide range of frequencies at high wattage. He reported that these devices were put into the field rather quickly without any real studies conducted as to the long term effects on health. Gunners were directly exposed to the ECMs, and when they were running he could actually hear a buzzing sound inside the head phones he wore for internal vehicle communications. Upon returning home he suffered constant headaches, difficulty thinking clearly, nausea and tinnitus. He was treated for post-traumatic stress syndrome, but believes these symptoms arose because of the RF exposure. It is interesting and relevant that Westhoff et al. (29) recently published a report of six soldiers in two separate incidents who experienced nausea and headache during an ECM mission in southwest Asia. Their symptoms were dismissed by the military authorities who concluded “the symptoms could not be linked with exposure to the HPM (high-power microwave) systems in any manner ‘consistent with current scientific literature’”.

A different DL, age 34, worked in information technology but developed insomnia and headaches. He discovered the cause was a DECT cordless phone, which caused tinges in his vision and severe headaches. These symptoms disappeared within 12 h after the DECT phone was turned off. Shortly after that he noticed intolerance to his laptop, and then over a period of 6 months developed difficulties in concentration. He noticed heart palpitations when he was close to the cordless phone base or laptop. This evolved within a recent period of being intolerant of his neighbor’s WiFi, but again he got relief when it was turned off. He is currently in good health as long as he stays away from sources of RF.

JJ, a civil engineer, and his wife live in California. Both were in excellent health. They went on vacation, and when they returned found that they both suffered from intense headaches, heart palpitations, tinnitus and insomnia while in their home, with relief when they left their home. Without their knowledge while they were away a rack of wireless smart meters had been installed directly below their bedroom. It took 4 months to get the utility to remove the smart meters, but by that time both had become electro-hypersensitive. This resulted in splitting headaches if using a cell phone, and it was painful to be in a WiFi environment or use a computer. The symptoms have not diminished over time if either is in an RF environment.

Discussion

EMFs are almost never simple sine waves. Powerline EMFs also have many higher frequency RF components, transients, harmonics and resonance frequencies (30–33). Furthermore most RF EMFs are pulse-modulated and often on carrier waves (34). Some applications of RF EMFs, such as in smart meters, use atypical short pulses of RF of very high intensity but very brief duration of individual pulses.

Recent years have seen a marked increase in overall exposure to EMFs. Urbinello et al. (35) monitored RF exposures in several European cities and found that in 1 year there were increases of between 20.1 and 57.1%, with much of the increase coming from mobile phone base stations and public transport. In many countries “smart” meters are being placed on homes, apartments and business establishments which report electricity usage to the utility using RF EMFs. And the use of RF to monitor electrical usage is scheduled to increase significantly. As the “smart (or perhaps not-so-smart) grid” develops, each household application will have a Zigbee RF generator in every kitchen and laundry room appliance, with each appliance sending RF signals to the smart meter, which will send RF signals to the utility. This will significantly increase RF levels inside homes, adding to the WiFi and other existing sources.

The report by Lamech (10) raises the possibility that excessive exposure to RF, perhaps to some specific characteristic of the RF waveforms associated with smart meters, triggers the development of EHS. As stated in this paper “….since the beginning of installation of wireless smart meters in the state of Victoria, people from various regional and metropolitan areas, of all ages and during all

seasons have started to report symptoms from exposure to the meters' radiofrequency fields…, only 8% of cases stated that they had suffered from EHS prior to exposure to smart meters, which suggests that when it comes to wireless meters, the threshold for symptom development appears to be significantly lower compared to that for other wireless devices".

There has always been uncertainty over which characteristics of EMFs are most important with regard to human health effects. Because the mechanisms whereby these various adverse health outcomes arise are still not well understood, it is important to ask the question of which components pose the greatest risk, whether or not we are confident of the answer. Frey (36, 37) first suggested that peak power density was more important than average power density. Litovitz et al. (38) concluded that 60 Hz EMFs and RF EMFs do very much the same things, and later studies suggested that the low frequency, modulatory component of RF was particularly important (39). Others have implicated on-off transients, "dirty electricity" and other characteristics of the fields than the steady 50 or 60 Hz fields.

The typical exposure from a smart meter is less than that of use of a cell phone held to the head [see Table 1 in reference (40)], and like that from other sources of RF does decline rapidly with distance from the smart meter. However, the smart meter RF radiation is significantly different from many other forms of RF, in that it consists of brief but very high intensity pulses. Thus, whereas the average exposure over time is not excessive it appears possible that the high intensity pulses are responsible for the development of EHS. Brief intense pulses have been described as "dirty electricity" by Milham and Morgan (33), who suggest that many of the reported adverse effects of EMFs are due to these brief events, rather than the sine wave forms. Since brief transients are founds among all forms of EMFs, including power line frequencies, these events may be the more important variable.

Conclusion

The weight of evidence indicates that EHS is a real syndrome induced by exposure to either ELF or RF EMF. In some cases it results from a brief, high intensity exposure, whereas in others it appears to reflect ambient exposures, especially those of increasing intensity and perhaps of certain waveforms. Whether from acute high intensity exposure or ambient background exposure from cell towers, mobile phones, smart meters and other devices, it is clear that not everyone develops EHS, for reasons not well understood. Certainly more research is needed to understand exactly which of the components of EMF exposures pose the greatest danger to human health, and what biological mechanisms are responsible. But the important conclusion is that there is something about EMFs of various forms that do pose direct hazards to human health.

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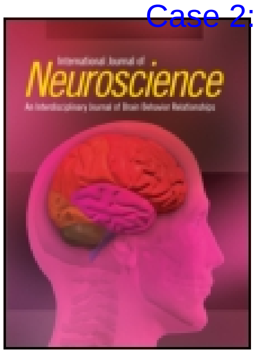

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Electromagnetic Hypersensitivity: Evidence for a Novel Neurological Syndrome

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Electromagnetic Hypersensitivity: Evidence for a Novel Neurological Syndrome

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ABSTRACT

Objective: We sought direct evidence that acute exposure to environmental-strength electromagnetic fields (EMFs) could induce somatic reactions (EMF hypersensitivity). *Methods*: The subject, a female physician self-diagnosed with EMF hypersensitivity, was exposed to an average (over the head) 60-Hz electric field of 300 V/m (comparable with typical environmental-strength EMFs) during controlled provocation and behavioral studies. *Results*: In a double-blinded EMF provocation procedure specifically designed to minimize unintentional sensory cues, the subject developed temporal pain, headache, muscle twitching, and skipped heartbeats within 100 s after initiation of EMF exposure ($p < .05$). The symptoms were caused primarily by field transitions (off–on, on–off) rather than the presence of the field, as assessed by comparing the frequency and severity of the effects of pulsed and continuous fields in relation to sham exposure. The subject had no conscious perception of the field as judged by her inability to report its presence more often than in the sham control. *Discussion*: The subject demonstrated statistically reliable somatic reactions in response to exposure to subliminal EMFs under conditions that reasonably excluded a causative role for psychological processes. *Conclusion*: EMF hypersensitivity can occur as a *bona fide* environmentally inducible neurological syndrome.

KEYWORDS: electromagnetic fields, evoked potentials, hypersensitivity, provocation study, sensory transduction, sleep study

INTRODUCTION

Man-made electromagnetic fields (EMFs) such as those produced by cell phones, powerlines, or computers are ubiquitous in the general and workplace environments. About 3%–5% of the population subjectively associates acute or subacute exposure to EMFs with departures from normal function or feeling (EMF hypersensitivity) (Levallois, Neutra, Lee, & Hristova, 2002; Schreier, Huss, & Röösli, 2006). The prevalence of self-reported EMF hypersensitivity has usually been attributed to somatization disorders (Rubin, Das Munshi, & Wessely, 2005; Rubin, Nieto-Hernandez, & Wessely, 2010).

A possible nonpsychological basis for EMF hypersensitivity was provided by the discovery of the ability of human beings to detect weak EMFs, as evidenced by the occurrence of field-onset and field-offset brain potentials (Carrubba, Frilot, Chesson, & Marino, 2007), and the induction of steady-state changes in brain electrical activity that persisted during the presence of the field (Marino, Carrubba, Frilot, Chesson, & Gonzalez-Toledo, 2010). The underlying mechanism of field sensory transduction appears to be an electric-force-sensitive ion channel (Marino, Carrubba, Frilot, & Chesson, 2009). Animal studies suggest that the electroreceptor cells and/or afferent processing cells are located in the brain stem (Frilot, Carrubba, & Marino, 2009, 2011).

Despite the physiological and biophysical evidence that could explain at least some cases of human somatic responses to EMFs without invoking psychological processes (Carrubba et al., 2007; Frilot et al., 2009, 2011; Marino et al., 2009, 2010), direct evidence of nonpsychological EMF hypersensitivity is lacking. Our purpose was to determine whether EMFs could

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produce symptomatic responses in a putatively hypersensitive subject while appropriately controlling for chance, confounders, and somatization.

METHODS

Subject

In the context of ongoing human, animal, and biophysical studies involving EMF sensory transduction in our laboratory, we were contacted by a 35-year-old female physician with multiple neurologic and somatic symptoms including headaches, hearing and visual disturbances, subjective sleep disturbances and nonrestorative sleep, and musculoskeletal complaints, all of which she reported could be precipitated by exposure to environmental EMFs and abated by withdrawal from the fields. Among the environmental triggering sources she identified were cell phones, computers, powerlines, and various common electrical devices. During extensive interviews she credibly explained the reasons for her belief that EMFs from common environmental sources could provoke her symptoms.

After she agreed to medical tests appropriate for evaluating her medical condition, she was admitted as a patient on the neurology service and underwent a physical exam including a comprehensive neurologic exam, a clinical electroencephalogram (EEG) exam, a noncontrast magnetic resonance (MR) imaging of the brain, an overnight sleep study (with video and expanded EEG montage) in which the resulting polysomnogram was scored in accordance with standardized rules (American Academy of Sleep Medicine, 2007), a standard laboratory evaluation of serum electrolytes and blood chemistries, liver function tests, serum fasting cortisol, and complete blood count, and direct evaluations of her EMF sensitivity in a series of EMF provocation and behavioral studies (see below). The institutional review board at the LSU Health Sciences Center approved all experimental procedures, and the subject gave her written informed consent.

EMF Exposure

The subject sat in a comfortable wooden chair with her eyes closed, and uniaxial 60-Hz (unless noted otherwise) sinusoidal electric fields were generated by applying a voltage to parallel 49-cm square metal plates spaced 36 cm apart (Figure 1). The equipment that controlled the field was located outside the subject's view and emitted no visual or auditory stimuli. The background electric field (the field present irrespective of whether or not a voltage was applied to the parallel plates) was about 1 V/m throughout the region occupied by the subject (HI-

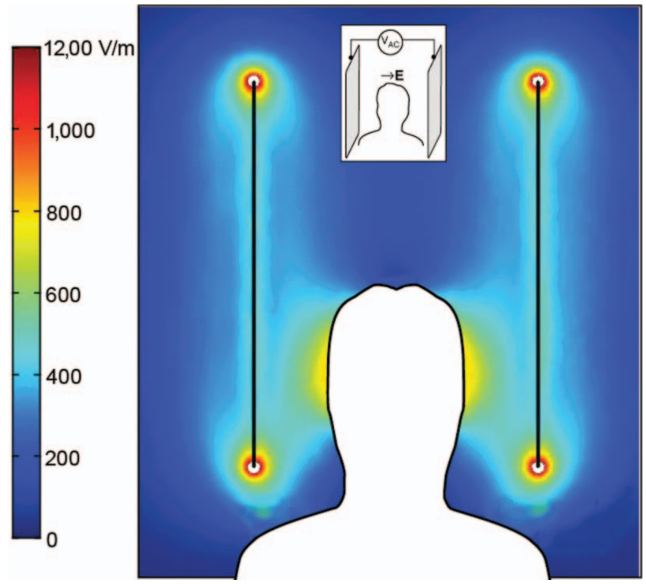

FIGURE 1. Spatial distribution of the external electric field (E) in the mid-sagittal plane. E was generated by applying $V_{AC} = 100$ volts to parallel metal plates while the subject was electrically isolated (insert), and calculated at all points in the subject's environment. Average E surrounding the head was about 300 V/m.

3603, Holaday, Eden Prairie, MN, USA). The plate arrangement did not produce magnetic fields. The continuously present background 60-Hz magnetic field was 0.1 mG, and the geomagnetic field was 599.8 mG, 68.4° below the horizontal component (component along the direction of the applied field, 360.5 mG) (MAG-03, Bartington, GMW, Redwood City, CA, USA). High-frequency signals from cell-phone towers and other distant antennae (1–10 GHz) were less than 0.1 μW/cm^2 (the background fields in the sleep-study room were similar; (Spectran, Aaronia, Euscheid, Germany).

In the provocation studies the electric field was applied for 100-s intervals with a duty cycle of 50% and a repetition rate of 10 Hz, which resulted in alternating field-on and field-off pulses of 100 ms (pulsed field); a continuous field (100% duty cycle) was used in one of the provocation studies. Duty cycle, pulse structure, and interval length were regulated by a microcontroller programmed to produce the desired signals. When the duty cycle was 50%, the actual EMF stimuli consisted of (1) 10 onset stimuli per second × 100 s = 1,000 field-onset stimuli per interval; (2) an equal number of field-offset stimuli; and (3) the presence of the EMF for a total of 50 s. When the duty cycle was 100%, there was only one field-onset stimulus and one field-offset stimulus, and the EMF was present for 100 s. In the behavioral studies, the electric field was applied in trials consisting of a 2-s epoch when a pulsed field was applied (50%

duty cycle, 10-Hz repetition rate) and a 10-s field-free control epoch.

Field Strength

The applied electric field was significantly distorted by the subject's body, resulting in strong inhomogeneities in the field surrounding the subject. To overcome the problem of measuring the external field, we used Maxwell's laws to calculate it at every point in the subject's vicinity. The subject was modeled as an electrically isolated composite of rectangular solids representing the trunk and lower extremities and an ellipsoid representing the head. The assumed conductivity was 1 S/m. The total electric field at every point was determined for $V_{AC} = 100$ V using finite-element analysis consisting of approximately 10^6 elements; a more detailed mesh was automatically generated in the head region (Multiphysics, Comsol, Los Angeles, CA, USA). The peak external electric field was about 1,000 V/m (see Figure 1); the average field was about 300 V/m around the head and less than 50 V/m around the body. The peak and average field strength and duration of exposure were far below the levels generally recognized as capable of producing physiological effects in human subjects (International Commission on Non-Ionizing Radiation Protection, 1998).

The external electric field resulted in an induced internal electric field in the brain in accordance with physical law. The strength of the induced brain electric field was comparable with that induced by environmental-strength power-frequency electric and magnetic fields (Carrubba, Frilot, Chesson, & Marino, 2010; Carrubba, Frilot, Hart, Chesson, & Marino, 2009).

Somatic Responses

A pulsed field (50% duty cycle) was applied for 100 s in 10 independent field-exposure intervals. The controls were ten 100-s sham-exposure intervals during which a field was not applied. The order of the field and sham intervals was determined randomly. The environmental conditions during the field-exposure and sham-exposure intervals were identical except that the wires carrying the plate voltage were disconnected during the sham-exposure intervals. At the end of each interval the subject was questioned by an interviewer blinded to whether or not the field had been applied and asked to describe any symptoms she developed during the interval, whether or not the symptoms had persisted into the interview period. She was queried using descriptive terms she had employed. Whenever she reported symptoms, commencement of the next interval was delayed until she reported that they had abated.

We used a pulsed field because we expected it would result in a stronger symptomatic response compared with a continuous field (Carrubba, Frilot, Chesson, & Marino, 2008; Frilot et al., 2011). To test this reasoning, we performed a second study to assess whether the subject developed a differential symptomatic response to the pulsed and continuous fields. The subject was exposed or sham exposed for 100-s intervals and immediately after each interval was interviewed as described above. A sham (S) field, continuous (C) field (100% duty cycle), and pulsed (P) field (50% duty cycle, 10 Hz) were applied, and the SCP pattern was repeated five times. The subject was blinded regarding the use of different EMFs; from her perspective, the laboratory procedures were identical to those followed in the first study. The interviewer was aware that the effects of C and P fields were being compared but was blinded regarding the actual sequence of the fields.

Behavioral Responses

We considered the possibility that any symptomatic response might be a result of the combined processes of conscious awareness of the EMF followed by a somatization reaction based on a fear that EMFs were harmful. We approached the issue by determining whether the subject could consciously perceive a field when it was presented in multiple independent trials. A field having the same strength and spatial distribution as previously (Figure 1) was applied in a series of trials each of which consisted of a 2-s epoch during which a pulsed field (50% duty cycle, 10-Hz repetition rate) was applied and a 10-s field-free control epoch. Eight independent sequences were employed, each with 30–50 trials. In three sequences, the frequency was 60 Hz; in two, it was 1 kHz; and in three others, the respective frequencies were 10, 100, and 500 kHz.

The subject held a small plastic box that housed a buzzer, a button labeled YES and another button labeled NO. In the middle of each on and off epoch the buzzer emitted a 4-kHz tone at 60 dB that lasted 100 ms, and she was instructed to press the YES or NO button whenever she heard the tone, depending on whether or not she had any conscious sensation of a field at that moment. Employing a custom-designed virtual instrument (LabView, National Instruments, Austin, TX, USA), we determined the number of YES and NO responses in the presence and absence of the field in each sequence. In addition, four sham sequences (minimum of 30 trials in each) were conducted in which a field was not applied. The subject had no knowledge that an off–on pattern was being used in the field sequences or that some sequences consisted of sham exposure.

TABLE 1. Polysomnography results. Comparison with usual night, per patient: "Same as usual." No epileptiform activity noted during arousals associated with unintended gross motor activity. Normal REM-related atonia

	Subject	Normal range
Sleep latency	6 min	13.4 ± 10.1 (Hirshkowitz, Moore, Hamilton, Rando, & Karacan, 1992)
Stage N1 sleep	13.8%	3%–8% (Chokroverty, Thomas, & Bhatt, 2005)
Stage N2 sleep	51.8%	44%–55% (Chokroverty et al., 2005)
Stage N3 sleep	23.6%	10%–15% (Chokroverty et al., 2005)
Stage R sleep	10.7%	20%–25% (Chokroverty et al., 2005)
REM latency	150.5 min	57%–66 min (Pressman, 2002)
WASO index	6/hr	1.3 ± 0.8 (Hirshkowitz et al., 1992)
WASO total	40.5 min	10.7 ±11 min (Naifeh, Severinghaus, & Kamiya, 1987)
Total sleep time	340.5 min	340.0 ± 70 (Hirshkowitz et al., 1992)
Sleep efficiency	88%	86.4% ± 11.6% (Hirshkowitz et al., 1992)
Arousal index	34.2/hr	16.8 ± 6.2 (Bonnet & Arand, 2007)
PLM index	7.8/hr	< 5/hr (Nicolas, Michaud, Lavigne, & Montplaisir, 1999)
AH index	0.2/hr	< 5/hr (American Academy of Sleep Medicine, 2005)

Note: REM, rapid eye movement; WASO, wake after sleep onset; PLM, periodic limb movement; AH, apnea/hypopnea.

Statistics

The frequencies of the somatic and behavioral responses in the presence and absence of the field were evaluated using the chi-square test (2 × 2 tables) or the Freeman–Halton extension of the Fisher exact probability test (2 × 3 tables; Freeman & Halton, 1951).

RESULTS

Clinical Studies

The patient's physical examination was unremarkable. The presence of frequent subjective awakenings from sleep, sometimes with unintended gross motor activity such as muscle twitching and leg jerking, prompted clinical concern for a sleep-related movement disorder, parasomnia, or nocturnal epilepsy. The polysomnogram revealed significant sleep fragmentation and discontinuity (Table 1) but no evidence of significant sleep-disordered breathing, nocturnal epilepsy, or abnormal rapid-eye-movement-related (REM-related) atonia. Periodic limb movements were noted but did not appear to be a major sleep-disrupting force.

Standard and 24-hr video-accompanied EEG recordings revealed normal-appearing background rhythms and no epileptiform activity. EEG performed in the presence of active cellular telephone use provoked a right-sided headache, but produced no unusual EEG waveforms. The MR image revealed evidence of cortical dysplasia in the right temporal lobe, and right parietal polygyria, both without interval change when compared with a study performed 19 months earlier. Laboratory evaluation for common metabolic/endocrine problems and blood count abnormalities was unremarkable.

Somatic Responses

The sequence and characteristics of the symptomological and behavioral experiments are shown in Table 2.

The question of a relation between the presence of the field and the occurrence of symptoms was directly addressed by interviewing the subject immediately following 100-s field-exposure or sham-exposure intervals; both the interviewer and the subject were blinded regarding the exposure condition. During the interviews, the subject reported a range of symptoms including localized pain in her jaw, ear, or the side of her head, a more diffuse head pain, and muscle pain or twitching in the hip, neck, and back. Sometimes she qualified the symptom as "strong" or "mild," and sometimes she denied all symptoms. We grouped the symptoms related to localized head pain as "temporal pain," those related to diffuse head pain as "headache," and those related to muscle effects as "muscle pain/twitching." Symptoms reported more rarely were indicated explicitly (see Table 3a). The subject consistently reported pronounced symptoms that occurred during the field intervals, particularly in intervals 7, 13, 14, 15, and 18. In the sham intervals, she reported no symptoms in intervals 4, 6, 8, 16, and 20; weak temporal pain in intervals 2, 3, and

TABLE 2. Sequence and characteristics of experiments

Experiment	Electric field Condition	No. of trials	Trial Duration (sec)	Response
1	Pulsed	10	100	Symptoms
	Sham	10	100	
2	Pulsed	5	100	Symptoms
	Continuous	5	100	
	Sham	5	100	
3	Pulsed	300	1	Behavior
	Sham	150	1	

TABLE 3. Evaluation of the relation between presentation of a pulsed electric field and the development of symptoms. (a) Results from the individual 100-s exposure intervals. (b) Summary table

(a)	Interval no.	Condition	Result
	1	Pulsed field	Temporal pain
	2	Sham	Mild temporal pain
	3	Sham	Mild temporal pain
	4	Sham	No symptoms
	5	Pulsed field	Temporal pain; headache
	6	Sham	No symptoms
	7	Pulsed field	Skipped heartbeats; feeling unease
	8	Sham	No symptoms
	9	Pulsed field	Headache
	10	Sham	Mild headache
	11	Pulsed field	Temporal pain
	12	Sham	Mild headache
	13	Pulsed field	Muscle twitch; feeling unease
	14	Pulsed field	Strong headache
	15	Pulsed field	Strong headache
	16	Sham	No symptoms
	17	Pulsed field	Stiff neck
	18	Pulsed field	Muscle twitch; temporal pain
	19	Sham	Mild temporal pain
	20	Sham	No symptoms

		Symptoms		
(b)	Field condition	None	Mild	$\geq$ Mild
	Sham	5	5	0
	Pulsed field*	0	0	10

*$p < .05$.

TABLE 4. Evaluation of the comparative effect of continuous and pulsed fields relative to a sham field on the development of symptoms. (a) Results from individual 100-s exposure intervals. (b) Summary table

(a)	Interval no.	Condition	Result
	1	Sham	No symptoms
	2	Continuous field	No symptoms
	3	Pulsed field	Temporal pain
	4	Sham	No symptoms
	5	Continuous field	No symptoms
	6	Pulsed field	Mild headache
	7	Sham	Mild headache
	8	Continuous field	Muscle twitch
	9	Pulsed field	Severe pain
	10	Sham	No symptoms
	11	Continuous field	Temporal pain
	12	Pulsed field	Headache; muscle twitch
	13	Sham	No symptoms
	14	Continuous field	Mild temporal pain
	15	Pulsed field	Mild temporal pain

		Symptoms		
(b)	Condition	None	Mild	$\geq$Mild
	Sham	4	1	0
	Continuous field	2	0	3
	*Pulsed field	0	2	3

*$p < .05$.

19; and a weak headache in intervals 10 and 12. The field and sham distributions of symptoms differed significantly ($p < .05$; see Table 3b).

In a second study, the relative role of EMF changes (number of onsets and offsets) and steady-state presence of the EMF were directly addressed by interviewing the subject immediately following 100-s exposure intervals in which either a pulsed field or a continuous field was presented. She was queried regarding her symptoms as previously and reported symptoms in both field intervals (see Table 4a). The symptoms triggered by the pulsed field were more intense compared with the sham control ($p < .05$; see Table 4b); the symptoms triggered by the continuous field did not differ from the sham control ($p = .16$). The subject reported no symptoms in four of five sham intervals (intervals 1, 4, 10, 13).

Behavioral Responses

The possible influence of conscious awareness of the EMF on the development of symptoms was investigated by assessing whether the subject could consciously perceive the field. A total of 300 independent trials involving carrier frequencies of 60 Hz to 500 kHz were used; the controls consisted of 150 sham trials. The results did not depend on the carrier frequency, and consequently the data were combined for analysis (see Table 5).

The subject failed to respond to the tone seven times while the field was on and seven times while it was off, resulting in a total of 293 responses for each of the two conditions. There were no missed responses in the sham conditions. The overall YES response rate in the field trials was $(51/586) \times 100 = 8.7\%$. The occurrence of a YES response was significantly associated with the presence of the field ($p < .05$; see Table 5a), but the sensitivity of the YES responses was low ($[32/(32 + 261)] \times 100 = 11\%$). The YES response rate in the sham trials was slightly higher than that seen in the field trials ($[27/273] \times 100 = 9.9\%$) (see Table 5b).

Table 5. Evaluation of conscious perception of a pulsed electric field. The subject's responses during the presence (on) and absence (off) of the field, respectively

		Pulsed field	
(a)	Response	On	Off
	Yes*	32	19
	No	261	274
		Sham	
(b)	Response	On	Off
	Yes	15	12
	No	135	138

*$p < .05$.

DISCUSSION

Appropriately controlled provocation studies are required to establish the existence of EMF hypersensitivity and to understand the relative importance of psychological and nonpsychological processes in mediating any observed symptoms. A working laboratory definition of EMF hypersensitivity formulated in symptomological terms is therefore needed to permit recognition of hypersensitivity reactions when they occur. In previous provocation studies, the assumption was made that true hypersensitive subjects would exhibit more or less the same symptoms in response to repeated provocations. The assumption led to experimental designs that involved averaging across exposed and control groups, which is an inherently insensitive statistical procedure for detecting real but variable responses (Rubin et al., 2005, 2010). The assumption is particularly inapplicable to EMF hypersensitivity because intrasubject and intersubject variabilities are its salient features (Levallois et al., 2002; Schreier et al., 2006). We defined EMF hypersensitivity as the occurrence of any medically recognized symptom in response to provocation using an environmentally relevant EMF; there was no requirement that the same symptom must reoccur when the EMF provocation was repeated. This definition avoided the problem of masking real effects and more appropriately matched the laboratory procedure to the known characteristics of EMF hypersensitivity (Levallois et al., 2002; Schreier et al., 2006). We focused on a single self-reported subject and employed a procedure in which she served as her own control. While controlling for artifacts, chance, and somatization, the question whether she reliably exhibited *any* symptomatic responses to an EMF was addressed; the alternative hypothesis was that she did not exhibit EMF-triggered symptoms. The laboratory conditions were controlled in such a way that a putative role of psychological processes could reasonably be identified.

The subject developed symptoms in association with the presentation of a pulsed electric field significantly ($p < .05$) more often than could reasonably be explained on the basis of chance (see Table 3). Several considerations suggested that the statistical link was a true causal association with a subliminal EMF. First, the subject's environment was carefully controlled to avoid putative confounding factors. The testing took place in an acoustically quiet environment, and the presence of uncontrolled environmental EMFs was nil. The environmental conditions during the field-exposure and sham-exposure intervals were identical except that during the sham-exposure intervals, at a point far removed from the subject's field of view, the wires carrying the plate voltage were disconnected. A key aspect of our laboratory procedure was the elimination of sensory cues that could serve as conscious markers of the electric field leading to a somatization reaction. All appropriate precautions were taken to eliminate potential confounders. Second, the occurrence of symptoms was significantly associated with the type of EMF (see Table 4). The symptomatic response was associated with the pulsed EMF, which maximized occurrence of the number of transient changes in the EMF (off–on and on–off), not with the presence of the field, as expected on the basis of prior animal studies where the issue of somatization was irrelevant (Frilot et al., 2011). Finally, in a behavioral study specifically designed to assess awareness of the field, YES response rates were 8.7% and 9.9% in the field and sham conditions, respectively, which provided no evidence for a psychological role in the development of the subject's symptoms. We therefore conclude with a reasonable level of certainty that the causal association we found between the presence of the EMF and the subject's symptoms was mediated by a subconscious neural process. Although chance was an unlikely explanation for the association, that possibility could not be excluded. The existence of the neurological syndrome reported here was previously suspected but not documented.

The mechanism for the subject's symptoms of headache, visual disturbances, and somatic musculoskeletal discomfort following exposure to EMFs is unknown. On the basis of clinical evaluation, intermittent seizure activity is not a credible explanation, although a deeper epileptic focus with partial seizure activity may have escaped the detection of surface EEG electrodes. The abnormal findings in the subject's medical workup included the abnormal MR image (cortical dysplasia and polygyric changes) and extensive sleep discontinuity and fragmentation manifested in the overnight polysomnogram; the possible association of these

findings with the subject's syndrome of EMF hypersensitivity is unknown.

Our aim here was to concentrate on the previously unaddressed question whether acute exposure to weak EMF could produce real but not precisely predictable somatic effects mediated by nonpsychological processes. Within the limitations of the study, we concluded that we demonstrated the neurological syndrome in the subject we studied. The question of whether EMF hypersensitivity is a significant public-health problem was not addressed here. The EMF we employed was equivalent in strength and pulse structure to EMFs pervasively present in the environment (Levallois et al., 2002; Schreier et al., 2006), and our results were consistent with the possibility that environmental EMFs can directly trigger clinical symptoms. Nevertheless resolution of the public-health issue depends on a deeper understanding of how internal EMFs caused by environmental EMFs are related to physiological process and of the role of psychological factors and comorbidities in the exposed population in exacerbating the processes resulting in disease.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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CARPENTER DEPO
EXHIBIT 11

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Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission

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ABSTRACT

Background: In 2011, IARC classified radiofrequency radiation (RFR) as possible human carcinogen (Group 2B). According to IARC, animals studies, as well as epidemiological ones, showed limited evidence of carcinogenicity. In 2016, the NTP published the first results of its long-term bioassays on near field RFR, reporting increased incidence of malignant glial tumors of the brain and heart Schwannoma in rats exposed to GSM – and CDMA – modulated cell phone RFR. The tumors observed in the NTP study are of the type similar to the ones observed in some epidemiological studies of cell phone users.

Objectives: The Ramazzini Institute (RI) performed a life-span carcinogenic study on Sprague-Dawley rats to evaluate the carcinogenic effects of RFR in the situation of far field, reproducing the environmental exposure to RFR generated by 1.8 GHz GSM antenna of the radio base stations of mobile phone. This is the largest long-term study ever performed in rats on the health effects of RFR, including 2448 animals. In this article, we reported the final results regarding brain and heart tumors.

Methods: Male and female Sprague-Dawley rats were exposed from prenatal life until natural death to a 1.8 GHz GSM far field of 0, 5, 25, 50 V/m with a whole-body exposure for 19 h/day.

Results: A statistically significant increase in the incidence of heart Schwannomas was observed in treated male rats at the highest dose (50 V/m). Furthermore, an increase in the incidence of heart Schwann cells hyperplasia was observed in treated male and female rats at the highest dose (50 V/m), although this was not statistically significant. An increase in the incidence of malignant glial tumors was observed in treated female rats at the highest dose (50 V/m), although not statistically significant.

Conclusions: The RI findings on far field exposure to RFR are consistent with and reinforce the results of the NTP study on near field exposure, as both reported an increase in the incidence of tumors of the brain and heart in RFR-exposed Sprague-Dawley rats. These tumors are of the same histotype of those observed in some epidemiological studies on cell phone users. These experimental studies provide sufficient evidence to call for the re-evaluation of IARC conclusions regarding the carcinogenic potential of RFR in humans.

1. Introduction

Early warnings on the potential carcinogenic risks of mobile phone radiofrequency radiation (RFR) raised in the early 2000 when, for the first time, it was published that people using mobile phones had a significant increased risk to develop vestibular Schwannoma and brain tumors (Hardell et al., 2003, 2002). In 2011, the International Agency for Research on Cancer (IARC) classified RFR as possible human carcinogen (Group 2B) based on limited evidence both in humans and experimental animals (Baan et al., 2011; IARC, 2013). Two epidemiological case-control studies resulted more informative for the IARC evaluation, showing that the risk to develop brain tumors and vestibular Schwannoma was increased in people with the highest cumulative use of mobile phones, in people who had used mobile phones on the

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same side of the head as that on which their tumor developed, and in people whose tumor was in the temporal lobe of the brain (the area of the brain that is most exposed to RFR when a wireless phone is used at the ear) (Hardell et al., 2011; Interphone study group, 2010). Another small case series study contributed to the IARC evaluation of evidence for an association of vestibular Schwannoma with mobile phone (Sato et al., 2011). The IARC Working group also noted that well conducted mechanistic studies showed that RFR induced aneuploidy, spindle disturbances, altered microtubule structures or DNA damage in several in vivo and in vitro models (IARC, 2013). Nevertheless, the IARC Working Group evaluated the overall evidence from mechanistic studies as inconclusive (IARC, 2013).

Experimental studies defining the potential carcinogenic effects of exposure to RFR have been largely inadequate because of the exposure conditions applied, because of the limited number of animals used in each experimental group and because of the short duration of the experiments. Since the late 90's, the need for well-conducted studies on laboratory animals has been identified by several public health institutions, including the World Health Organization and the US Food and Drug Administration (FDA, 1999; Repacholi, 1997). Indeed the conduct of cancer bioassays with RFR presents challenges that are not ordinarily met in studies with chemical or other physical agents. For example, the radiation frequency is an important determinant of the specific absorption rate (SAR). The whole-body SAR provides little information about spatial or organ-specific energy deposition, as it strongly depends on field polarization and animal posture. Furthermore, long-term exposure to RF radiation at a fixed frequency and power density will result in substantial changes in SAR over time as an animal gains body weight. Even if the power is adjusted for body weight changes, the spatial distribution can vary (IARC, 2013). Although SAR is a key parameter for thermal RFR effects, several other parameters of RFR exposure such as exposure duration, frequency, polarization, modulation, and environmental magnetic fields are of importance for biological RFR effects (IARC, 2013; Belyaev, 2010). In addition physiological parameters, which may vary in development and between individuals, are of importance (IARC, 2013; Belyaev, 2010). Variability of physiological parameters need to be addressed in long-term bioassays using a large group of animals adequately randomized.

Following the nomination to study cell phone radiofrequency radiation made by the U.S. Food and Drug Administration, the US National Toxicology Program (NTP) started a large systematic and integrated experimental project on RFR, including in vivo long-term bioassays in Harlan Sprague-Dawley (HSD) rats and B6C3F1/N mice exposed to RFR from prenatal life up to 2 years in the situation of near field, reproducing the exposure to RFR generated by the antenna of mobile phone (Wyde et al., 2016).

In 2005, the Ramazzini Institute (RI) started a life-span carcinogenic study on Sprague-Dawley rats to evaluate the carcinogenic effects of RFR in the situation of far field, reproducing the environmental exposure to RFR generated by an 1.8 GHz GSM antenna of the radio base stations of mobile phone (Soffritti et al., 2006, 1999). This is the largest long-term study ever performed in rats on the health effects of RFR, including 2448 animals. The plan of the experiment is reported on Table 1.

The elaboration of the NTP studies have been already completed and a report of partial findings has been recently published (Wyde et al., 2016). The communication of the first important findings of the study was urged by two factors: 1) the fact that also a small increase of the incidence of tumors induced by the exposure to RFR could have great impact for public health; and 2) because the tumors of the brain and heart observed at low incidence in male rats exposed to Global System for Mobile Communications (GSM) – and Code Division Multiple Access (CDMA) – modulated cell phone RFR in the NTP study are of the type similar to the ones observed in some epidemiological studies of cell phone users. Interim cohorts were also examined for evidence of RFR-induced genotoxicity: DNA damage was significantly increased in

Table 1
Long-term bioassay on 1.8 GHz base station RFR, administered at different doses to Sprague-Dawley rats, from prenatal life to spontaneous death: plan of the experiment (Experiment BT 1CEMRF).

Group	Treatment	Animals	
No.	GSM-RFR 1.8 GHz (V/m)[a]	Sex	No.
I	0	M	412
		F	405
		M + F	817
II	5	M	401
		F	410
		M + F	811
III	25	M	209
		F	202
		M + F	411
IV	50	M	207
		F	202
		M + F	409
Total			2448

[a] Treatment with GSM-RFR 1.8 GHz for 19 h/day started on the 12th day of pregnancy and lasted until natural death for groups I, II, III, IV.

the frontal cortex of male mice (both CDMA and GSM), peripheral leukocyte of female mice (CDMA only) and hippocampus of male rats (CDMA only) (Smith-Roe et al., 2017). Previous studies have also shown that RFR might disrupt the blood-brain barrier. (Nittby et al., 2008).

The elaboration of the RI study data is still ongoing. However, partial findings are now available and, for the same reasons reported by the NTP, we felt motivated to publish urgently the final results on brain and heart tumors.

2. Materials and methods

2.1. 1.8 GHz base station exposure system and facilities

In order to expose the animals to a mobile phone radiofrequency field representative of a 1.8 GHz base station, a specific radiation system, totally representative of the real environmental situation present in geographic areas close to GSM base station radiation emissions (Fig. 1). The exposure system was designed and constructed by TESEO S.P.A. Company, Turin, Italy. The field generation, in order to be representative of a real GSM field emission, has been modulated in GMSK mode, in CalI operating mode and with the complete Time Slot

assignment. The field emission has been determined in the frequency of 1835 MHz, normally used for GSM services. The intensity ofthe fields generated in the test areas can be defined in the 1–50 V/m range. The RF generation units regulates the output RF levels using a closed loop control system, able to stabilize the generated RF level in an uncertainty level of 1 dB range.

The rats were located in 4 rooms with the same environmental conditions (i.e. temperature of 22 ± 3 °C, a relative humidity of 40–60% and 12 h/day homogeneous diffusion of light). The exposure rooms were totally shielded with RF absorbing material (Hyfral APM12) in order to minimize the effect of field non-uniformity due to reflections and consequent interferences caused by the walls. The shielded rooms ensured a minimum insulation of 30 dB. The rat cages were located in wooden circular-shaped devices. Each single exposure devices served at least 400 rats. All devices were identical and a different intensity of RFR was provided as reported by the experimental design. The exposure system included the following parts: 1) main generator unit; 2) external control panel; 3) main radiator system (transmitting antenna); 4) feedback probe

1) The main generator unit was assembled in a metallic crack to

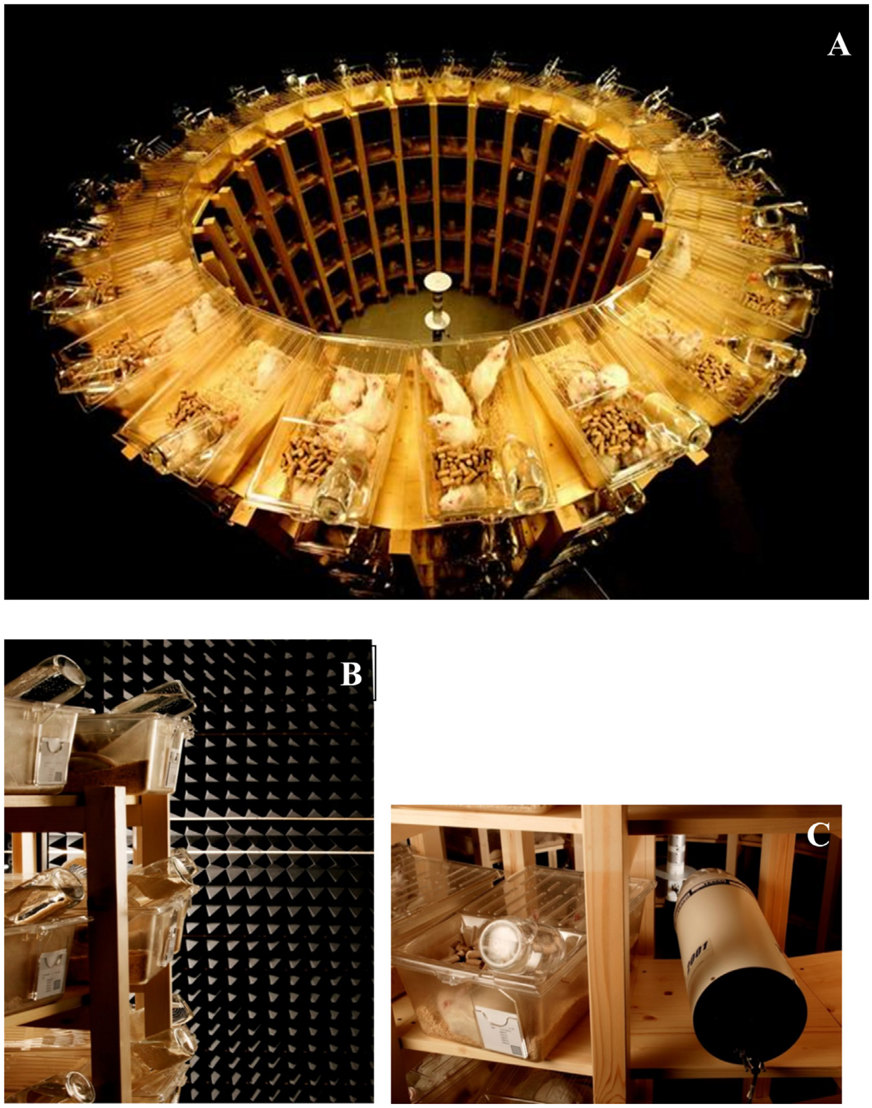

Fig. 1. RI study on 1.8 GHz base station RFR: exposure system. The rat cages were located in wooden circular-shaped devices, as in a sort of condominium. Each single exposure device served at least 400 rats (A). The exposure rooms were totally shielded in order to minimize the effect of field non-uniformity due to reflection and consequent interference caused by the walls (B). Detail of the RFR feedback probe used to measure the field (TESY2001 field sensor) and of the animal cage with methacrylate markers, cover and mangers (C).

produce the following functions: a) generate a GSM signal, with complete channel simulation capability and frequency preselection; b) signal pre – amplifications – age, with gain regulation input; c) final stage, dimensioned for a total power output of plus 50 dBm; d) reference signal loop back input, for closed loops power control; the control was closed at the antenna connection level in order to stabilize at the maximum level the radiation unit RF feed; e) power supply unit; f) cooling unit for continuous use of the device.

2) The external control panel was installed to ensure the personnel health. The exposure system status was controlled using an external control panel installed on the wall in proximity of the room door. The panel was connected to the main unit using a multiple wire, terminated with connectors.
3) The main radiation system was connected to the main generator unit through a low loss coaxial cable. The RFR emission was radiated to the cage using a collinear antenna (a phased array of stacked dipoles) installed in the center of the cage devices. The about radiator was able to transmit an homogeneous RFR far field (with cylindrical distribution of the strength) and shape able to cover the complete height of the cage devices. A reflector, installed on the top of the radiator reduced the vertical emission lobe. Part of the RF power feeding the radiator unit was coupled using a splitter; this signal was used to feed the closed loop level control system installed in the tower rack. The rat cages were distributed on dielectric structures with circular profile; the RF radiator has been installed in the center of each structure. Animals were located on five levels up to a height of about 1.6 m. Each level forms a ring within the toroid at a distance of about 2 m from the toroid center. The horizontal radiation polar diagram of the system allow a total field uniformity better than 3 dB on the total exposure surface. The radiation pattern on the vertical section of the exposure area has a cardioids shape; the vertical opening angle allow a field uniformity better than 3 dB on the exposed area
4) Monitoring probe. The method applied for the measurement of the RFR was completely in compliance with the measurement standards generally applied during "on–site" GSM measurement and evaluation. The about mentioned standard in Italy has been defined in detail in the D.L. 381/98 that outlines the timing and procedures to apply during this measure. The probe used to measure the field was the TESY2001 field sensor. The probe was linked to a personal computer and it was able to show continuously the field intensity value updated every 10 s. The TESY2001_WIN software was used to control the probe, to download the recorded information and produce diagrams of thee field values of the day, week or month.

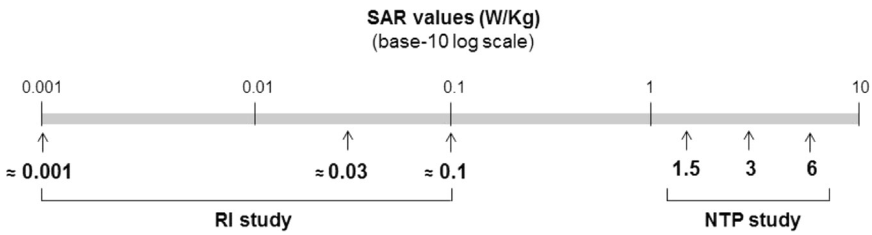

Fig. 2. Comparison between the estimated SAR levels of the RI study (far-field RFR) and the SAR levels of the NTP study (near-field RFR). The estimated exposure SAR levels of the Ramazzini Institute study (0.1 W/Kg, 0.03 W/Kg, 0.001 W/Kg) are significantly lower than the ones used by the NTP (6 W/Kg, 3 W/Kg, 1.5 W/Kg).

The exposure system was positively evaluated by representatives of the US National Institute of Standards and Technology and the US National Institute of Environmental Health Sciences.

2.2. Diet

All the animals received standard feed administered in pellets ad libitum and provided by the "Laboratorio Dottori Piccioni" (Milan, Italy), the formulation being certified for each supply used at the Cesare Maltoni Cancer Research Center of the RI (CMCRC/RI) over a period of more than 40 years. All the animals received tap water ad libitum. Both feed and water were periodically analyzed to exclude the presence of contaminants.

2.3. Experimental animals

Sprague-Dawley rats from the same colony used for more than 40 years at the CMCRC/RI were used as experimental animals. The basic expected spontaneous tumor incidence and its fluctuations were based upon data derived from more than 20,000 historical controls.

The animals in experiment were generated in the following way: 1) inbred males and females of the experimental animals used to generate the breeders, were randomized in 4 groups avoiding to have more than 1 brother or sister per group. The size of the breeder groups was proportional to the member of offspring required for the experiment; 2) mating of the studies who generated the experimental animals was strictly outbred (mode possible by pedigree identification number of each animal); 3) all offspring of each litter of these breeders were assigned to the respective planned experimental group.

The experimental animals were identified by ear punch (Jackson Laboratory method) and distributed by sex, litter by litter, until the planned number for each group was reached. After weaning, animals received ordinary feed and water ad libitum. Animals were housed 5 per cage, in polycarbonate cages (41 × 25 × 15) and a shallow layer of white wood shavings as bedding. In order to minimize dispersion and interferences, no metal cage accessories were used and instead methacrylate markers, cover and mangers were adopted. All the animals were kept in a temperature-controlled environment at 22 ± 3 °C and 40–60% relative humidity, with 12 h/daylight/dark alternation.

The experiments were conducted according to the current (2005–2008) Italian law regulating at the time, the protection of animals used for experimental and other scientific purposes (Legislativo, 1992). The experiment was performed following the principles of Good Laboratory Practice (GLP), with the same standard operating procedure described in our previous studies (Soffritti et al., 2016a, 2016b).

2.4. Treatment

Four groups of 817, 811, 411, 409 male and female Sprague-Dawley rats of our colony were exposed from prenatal life (12th day of mother gestation) until natural death to a 1.8 GHz GSM far field respectively of 0 (control, sham exposure), 5, 25, 50 V/m with a whole-body exposure for 19 h/day, using the remaining 5 h for maintenance purposes, like feed and water refill, cage cleaning, test system verification and check of the health of animals. The plan of the experiment is reported on Table 1.

2.5. Statistical analyses

Statistical analysis for possible differences in survival times was based on Kaplan-Meier survival curves evaluated by Log-rank tests, as well as on the Cox proportional hazard regression model (Cox, 1972). To highlight possible differences in the incidence of tumors among treated groups and controls or among different treated groups, Chi-squared and Fisher tests were performed. The Chi-squared test was used when the number of tumors was higher than 5 in all groups; in all other cases Fisher's Exact test was used. The level of significance was set at $p \leq .05$. The statistically significant p-values found are reported in the tables. The presence of a linear trend in tumor incidences was evaluated by the Cochran-Armitage trend test with a level of significance set at $p \leq .05$.

2.6. SAR estimates

SAR estimation has been performed in collaboration with Dr. Franco Maroglio (TESEO S.p.A. Company, Turin, Italy.) and Dr. Perry Wilson (US National Institute of Standards and Technology). The SAR estimate was obtained multiplying a far-field coupling factor (F) with the power density (E^2/η_0). A far-field coupling factor of 0.18 W/Kg/(mW/cm^2) for the rat whole body SAR was derived from previous estimates (Anderson et al., 2004), while η_0 is the free-space impedance ($\eta_0 = 377\,\Omega$). For $E = 50$ V/m, we get a power density ($E^2/\eta 0$) of 0.66 mW/cm^2 and a whole body SAR of 0.1 W/Kg (0.18 × 0.66). For 25 V/m, we get a power density of 0.17 mW/cm^2 and a whole body SAR of 0.03 W/Kg. For 5 V/m, the power density will be 0.07 mW/cm^2 and the expected whole body SAR 0.001 W/Kg.

In Fig. 2a comparison between the estimated SAR levels of the RI study (far-field RFR) and the SAR levels of the NTP study (near-field RFR).

3. Results and discussion

3.1. Food and water consumption, body weight and survival

The experiment proceeded smoothly and no unexpected alteration in the clinical status of the animals was observed in the various groups. The biophase parameters for control and treated groups are presented in Fig. 3. No differences were observed in mean water consumption (A and B), food consumption (C and D), mean body weight (E and F) or survival index (G and H), either in male or in female rats.

3.2. Neoplastic lesions

In this article we are reporting the final results from the histopathological evaluation of all brains and hearts of treated and untreated animals. The estimated exposure SAR levels of the RI study (0.1 W/Kg, 0.03 W/Kg, 0.001 W/Kg) are significantly lower than the ones used by the NTP (6 W/Kg, 3 W/Kg, 1.5 W/Kg), but the time and length of exposure of the RI study (19 h/day, continuous exposure, 7 days/week, life-span) was longer than in the NTP study (18 h/day, 10 min on/10 mins off, 7 days/week, 104 weeks). The number of rats analyzed by the RI study (> 200 animals/sex/group, 4 groups, total 2448 animals) is also higher than the NTP study (90 animals/sex/group, 4 groups,

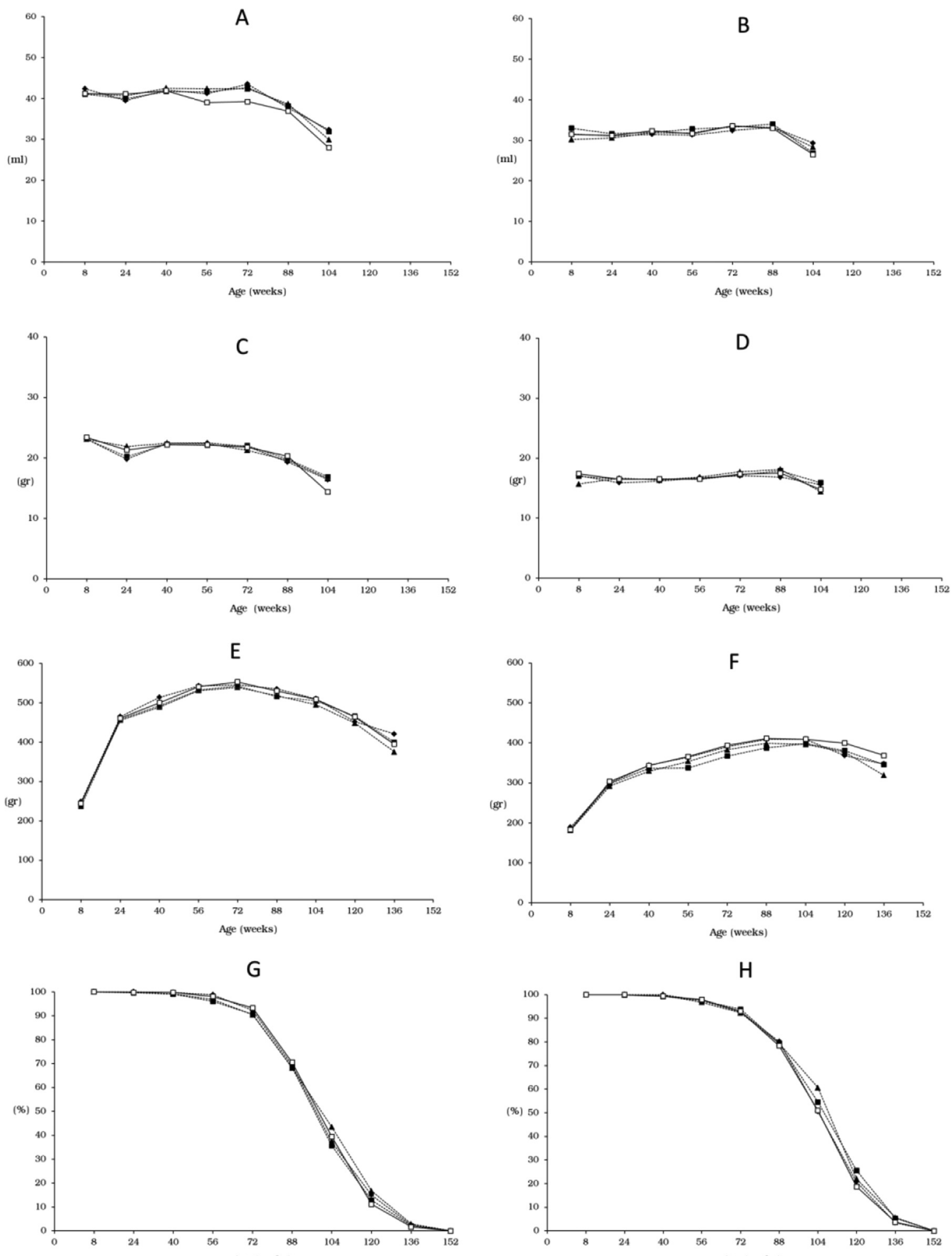

Fig. 3. Male (A) and female (B) water consumption, and male (C) and female (D) food consumption from 8 to 104 weeks of age; male (E) and female (F) mean body weight from 8 to 136 weeks of age; male (G) and female (H) survival index from 0 to 152 weeks of age. Data shown refer to control group (▢), 5 V/m (■), 25 V/m (▲), and 50 V/m (◆) treated group.

total 720 animals).

3.2.1. Pre-malignant and malignant lesions of the heart

The incidence of pre-neoplastic and neoplastic lesions of the heart are reported in Table 2. A statistically significant increase in the incidence of heart Schwannoma was observed in treated male rats at the highest dose: 0/412, 3/401 (0,7%), 1/209 (0,5%), 3/207 (1,4%) ($P < .05$; Fisher). Furthermore, an increase in the incidence of Schwann cells hyperplasia was observed in treated male rats at the highest dose, although this was not statistically significant: 3/412 (0,7%), 2/401 (0,5%), 1/209 (0,5%), 5/207 (2,4%). An increase in the incidence of Schwann cells hyperplasia was observed in treated female rats at the highest dose, although this was not statistically significant: 2/405 (0,5%), 0/410, 0/202, 2/202 (1,0%). Schwann cell hyperplasia or

Table 2

Long-term bioassay on 1.8 GHz base station RFR, administered at various doses to male (M) and female (F) Sprague-Dawley rats (Experiment BT 1CEMRF): results on pre-neoplastic and neoplastic lesions of the heart.

Group No.	Dose GSM-RFR	Animals		Hyperplasia Schwann cells		Endocardial Schwannoma		Intramural Schwannoma		Total Schwannoma	
	1.8 GHz (V/m)	Sex	No.	No.	%	No.	%	No.	%	No.	%
I	0	M	412	3	0.7	0	0.0	0	0.0	0	0.0
	(control)	F	405	2	0.5	0	0.0	4	1.0	4	1.0
		M+F	817	5	0.6	0	0.0	4	0.5	4	0.5
II	5	M	401	2	0.5	2	0.5	1	0.2	3	0.7
		F	410	0	0.0	2	0.5	7	1.7	9	2.2
		M+F	811	2	0.2	4	0.5	8	1.0	12	1.5
III	25	M	209	1	0.5	1	0.5	0	0.0	1	0.5
		F	202	0	0.0	0	0.0	1	0.5	1	0.5
		M+F	411	1	0.2	1	0.2	1	0.2	2	0.5
IV	50	M	207	5	2.4	2	1.0	1	0.5	3	1.4*
		F	202	2	1.0	1	0.5	1	0.5	2	1.0
		M+F	409	7	1.7	3	0.7	2	0.5	5	1.2

* Statistically significant $p \leq .05$ using Fisher exact test.

Schwannoma are two proliferative lesions of cardiac Schwann cells in rats (Alison et al., 1987; Novilla et al., 1991). In Sprague-Dawley rats, Schwannoma of the heart is a rare malignant tumor and it occurs more frequently in males rather than females. There are subendocardial and intramural variants of heart Schwannoma, with local invasion more common than distant metastases (Giovannini et al., 1999). Heart Schwannoma occurs in a variety of rat strains and has not been described in mice (Elmore et al., 2017). In a period of over 20 years (1984–2004), the data on historical control rats of the RI show that only 19 cases of Schwannoma have been reported out of 3160 untreated males (incidence 0,6%) and only 10 cases of Schwannoma have been reported out of 3165 untreated females (incidence 0,3%). The pathological diagnostic criteria of Schwann cell hyperplasia and Schwannoma of the heart have been recently revised by the NTP and the pathological diagnosis of the RI were performed in blind and in compliance with the most recent NTP recommendations and the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) guidelines (Berridge et al., 2016; Elmore et al., 2017). Furthermore, in order to harmonize the diagnostic criteria, the pathological lesions of the heart observed by the RI, on April 2017 have been screened for second opinion diagnosis in blind by NTP pathologists.

The RI findings on heart tumors are consistent with the results reported by the NTP (Wyde et al., 2016). In the NTP study, for both modulations (GSM and CDMA), there was a significant positive trend in the incidence of Schwannomas of the heart in rats with respect to exposure SAR (6 W/Kg, 3 W/Kg, 1.5 W/Kg). Additionally, the incidence of Schwannomas in the 6 W/Kg males was significantly higher in CDMA-modulated RFR-exposed males compared to controls. In the 6 W/Kg GSM-modulated RFR-exposed males the incidence was higher, but not statistically significant ($p = .052$) compared to controls. Schwann cell hyperplasia of the heart was also observed in three males exposed to 6 W/Kg CDMA-modulated RFR (Wyde et al., 2016).

Our findings are also consistent with the epidemiological evidence, where an increased incidence of tumors of the same cells, vestibular Schwannoma, had been associated with the use of mobile phones (Hardell et al., 2013). Schwannomas in humans might present pre-malignant characteristics: they can progress to malignant lesions (Hasegawa et al., 2013) and they often present molecular characteristics that a typical of pre-malignant lesions, such as aneuploidy (Warren et al., 2003). In particular, genetic factors (e.g. neurofibromatosis) and environmental factors (e.g. gamma radiation) can increase up to 10 fold the risk of malignant progression of vestibular Schwannoma (Seferis et al., 2014). The statistically significant increase in the incidence of heart Schwannomas observed in male rats in the late part of their life, both in the RI and NTP studies, are consistent with the epidemiological findings, where the highest increase in risk of vestibular Schwannoma among humans exposed to RFR was observed in men over 50 years of age with the highest cumulative exposure (Hardell et al., 2013, 2003).

3.2.2. *Pre-neoplastic and neoplastic lesions of the brain*

The incidence of pre-neoplastic and neoplastic lesions of the brain are reported in Table 3. No statistically significant increase in the incidence of pre-neoplastic and neoplastic lesions of the brain was observed. However, a non-statistically significant dose dependent increase in the incidence of malignant glial tumors was observed in treated female rats: 2/405 (0,5%), 3/410 (0,7%), 2/202 (1,0%), 3/202 (1,5%). No malignant glial tumors were observed in male controls (0/412) and only 2 malignant glial tumors were observed in female controls (2/405, incidence 0,5%). In a period of over 20 years (1984–2004), the data on historical control rats of the RI show that only 15 cases of malignant glial tumors have been reported out of 3165 untreated females (incidence 0,5%) (and 41 cases of malignant glial tumors have been reported out of 3160 untreated males, incidence 1,3%). Therefore, the incidence of malignant glial tumors observed in treated female rats is slightly increased, in particular at the highest dose, if compared with our historical controls. The pathological diagnostic criteria of malignant glial tumors have been recently revised by the NTP and the pathological diagnosis of the RI were performed in blind and in compliance with the most recent NTP recommendations and the INHAND guidelines (Elmore et al., 2017; Kaufmann et al., 2012). Furthermore, in order to harmonize the diagnostic criteria, the pathological lesions of the brain observed by the RI, on April 2017 have been screened for second opinion diagnosis in blind by NTP pathologists.

The RI findings on brain tumors are consistent with the results reported by the NTP (Wyde et al., 2016). In the NTP study, a statistically significant positive trend in the incidence of malignant glial tumors was reported only in male rats ($p < .05$) for CDMA-modulated RFR exposures. A low incidence of malignant glial tumors was observed in all groups of male rats exposed to GSM-modulated RFR and in different groups of female rats exposed to GSM-modulated RFR and CDMA-modulated RFR exposures. No malignant glial tumors were observed in controls (0/180). Also in the RI study, only 2 malignant glial tumors were observed among controls (2/817, incidence 0.2%), while a slightly overall increased incidence was observed in male and female treated rats (13/1631, incidence 0.8%). It is noteworthy that the estimated exposure SAR levels of the RI study (0.1 W/Kg, 0.03 W/Kg, 0.001 W/Kg) are significantly lower than the ones used by the NTP (6 W/Kg, 3 W/Kg, 1.5 W/Kg).

The increase in the incidence of malignant glial tumors observed in

Table 3
Long-term bioassay on 1.8 GHz base station RFR, administered at various doses to male (M) and female (F) Sprague-Dawley rats (Experiment BT 1CEMRF): results on pre-neoplastic and neoplastic lesions of the brain.

Group No.	Dose EMF-GSM 1.8 GHz (V/m)	Animals Sex	Animals No.	Meninges[a] Benign Tumors No.	Meninges[a] Benign Tumors %	Meninges[a] Malignant Tumors No.	Meninges[a] Malignant Tumors %	Glia[b] Glial cells hyperplasia No.	Glia[b] Glial cells hyperplasia %	Glia[b] Malignant Tumors No.	Glia[b] Malignant Tumors %
I	0	M	412	2	0.5	1	0.2	0	0.0	0	0.0
	(control)	F	405	0	0.0	1	0.2	1	0.2	2	0.5
		M+F	817	2	0.2	2	0.2	1	0.1	2	0.2
II	5	M	401	4	1.0	4	1.0	0	0.0	3	0.7
		F	410	4	1.0	1	0.2	0	0.0	3	0.7
		M+F	811	8	1.0	5	0.6	0	0.0	6	0.7
III	25	M	209	1	0.5	1	0.5	1	0.5	2	1.0
		F	202	2	1.0	0	0.0	0	0.0	2	1.0
		M+F	411	3	0.7	1	0.2	1	0.2	4	1.0
IV	50	M	207	2	1.0	0	0.0	0	0.0	0	0.0
		F	202	2	1.0	0	0.0	0	0.0	3	1.5
		M+F	409	4	1.0	0	0.0	0	0.0	3	0.7

[a] Benign and malignant tumors of the meninges include meningioma and granular cell tumors benign and malignant.
[b] Tumors of the glia include oligodendroglioma, astrocytoma, mixed glioma.

the RI experimental study, is consistent with the epidemiological evidence, where an increased incidence of brain tumors of a similar histotype, glioma, had been associated with the use of mobile phones (IARC, 2013; Carlberg and Hardell, 2017). Central nervous system (CNS) tumors are rare in rats(< 0,1%), nevertheless their importance as sentinel tumors in carcinogenesis bioassays has been proved fundamental, since different substances are able to induce increased incidence of these malignancies (Elmore et al., 2017).

4. Conclusions

In 2005, the RI started a life-span carcinogenic study on Sprague-Dawley rats to evaluate the carcinogenic effects of RFR in the situation of far field, reproducing the environmental exposure to RFR generated by 1.8 GHz GSM antenna of the radio base stations of mobile phone. This is the largest long-term study ever performed in rats on the health effects of RFR, including 2448 animals. In this article, we report the final results regarding brain and heart tumors. A statistically significant increase in the incidence of heart Schwannoma was observed in treated male rats at the highest dose (50 V/m). Furthermore, an increase in the incidence of Schwann cells hyperplasia was observed in treated male and female rats at the highest dose (50 V/m), although this was not statistically significant. An increase in the incidence of malignant glial tumors was observed in treated female rats at the highest dose (50 V/m), although this was not statistically significant. Similarly to the NTP (Wyde et al., 2016), the communication of the first important findings of the RI study was urged by different factors: 1) the fact that also a small increase of the incidence of tumors induced by the exposure to RFR could have great impact for public health; 2) The RI findings on far field exposure to RFR are consistent with the results of the NTP study on near field exposure to RFR (Wyde et al., 2016), as both reported an increase in the incidence of tumors of the brain and heart in RFR-exposed Sprague-Dawley rats;and 3) because the tumors of the brain and heart observed at increased incidence in rats exposed to RFR generated by an 1.8 GHz GSM antenna in our study are of the same cytological origin of those observed in some epidemiological studies of cell phone users. These experimental studies provide sufficient evidence to call for the re-evaluation of IARC conclusions regarding the carcinogenic potential of RFR in humans.

Acknowledgements

This article is in memory of Prof. Cesare Maltoni, who started this project a long time ago and left us the task of accomplishing it: we hope we have come up to his expectations. It is with a great sense of gratitude and recognition that we thank Dr. Morando Soffritti for his invaluable contribution to planning and conducting the experiments when he was Director of our Cesare Maltoni Cancer Research Center. We are grateful to all staff at the Laboratory of the CMCRC/RI for their commitment to conducting the experiments and finally making it possible to publish the results. We thank Dr. Livio Giuliani for his technical assistance and the TESEO S.P.A. Company, Turin, Italy

that designed and constructed the 1.8 GHz base station exposure system.

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Ethics review and approval

The experiments were conducted according to the Italian law regulating, at the time, the protection of animals used for experimental and other scientific purposes (Decreto Legislativo, 1992).

Disclosure statement

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper. They also declare that their funding sources had no direct role in the study design, data collection, analysis and interpretation of the data, in the writing of the manuscript, or in the decision to publish the work.

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EXHIBIT 12

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Magnetic field exposure and long-term survival among children with leukaemia

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We examined the association between magnetic field (MF) exposure and survival among children with acute lymphoblastic leukaemia (ALL) treated at 51 Pediatric Oncology Group centres between 1996 and 2001. Of 1672 potentially eligible children under treatment, 482 (29%) participated and personal 24-h MF measurements were obtained from 412 participants. A total of 386 children with ALL and 361 with B-precursor ALL were included in the analysis of event-free survival (time from diagnosis to first treatment failure, relapse, secondary malignancy, or death) and overall survival. After adjustment for risk group and socioeconomic status, the event-free survival hazard ratio (HR) for children with measurements $\geqslant 0.3\,\mu T$ was 1.9 (95% confidence interval (CI) 0.8, 4.9), compared to $<0.1\,\mu T$. For survival, elevated HRs were found for children exposed to $\geqslant 0.3\,\mu T$ (multivariate HR = 4.5, 95% CI 1.5 – 13.8) but based on only four deaths among 19 children. While risk was increased among children with exposures above $0.3\,\mu T$, the small numbers limited inferences for this finding.
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Two pooled analyses have reported a positive association between childhood leukaemia incidence and residential magnetic fields (MFs) in the upper tail of the exposure distribution (Ahlbom *et al*, 2000; Greenland *et al*, 2000). However, *in vitro* studies and *in vivo* animal experiments have not produced evidence of adverse effects at or near the MF levels associated with residential environments, nor has a biophysical basis for such effects been established (NIEHS, 1998; McCann *et al*, 2000). While earlier studies have examined potential effects of MF exposure on leukaemia incidence, MF research has not focused on the progress of disease. We have examined our hypothesis that if environmental exposure to MF influences leukaemia blast cells following tumour initiation, effects on relapse and survival in newly diagnosed acute lymphoblastic leukaemia (ALL) may be evident.

MATERIALS AND METHODS

Study subjects

Eligibility criteria included a diagnosis of B-precursor, T-cell, or B-cell ALL within the previous 12 weeks, age between 1 and 15 years, enrolment into a Pediatric Oncology Group (POG) treatment protocol at a participating centre, and an adult family member who speaks English, Spanish, or French. Pediatric Oncology Group was a National Cancer Institute-sponsored consortium that represented approximately half of all centres that treated childhood cancer in North America. The study protocol was approved by the institutional review boards of the Public Health Institute and each participating treatment centre.

Health professionals at POG centres introduced the study to eligible children and their families, and obtained written informed consent from interested families. During the accrual period of September 1996 to January 2001, 1672 children were being treated on therapeutic protocols at the 51 participating POG centres. Twenty nine per cent (482) of children enrolled into our study. The study group was similar in gender and age to the cohort of eligible children, although percentages of children by race/ethnicity differed: white children 72% (cohort) *vs* 61% (potentially eligible), Hispanic children 15 *vs* 21%, African-American children 7 *vs* 9%.

Families were contacted within 14 days of an agreement to participate by staff at the Public Health Institute for administration of a structured telephone interview and explanation of the exposure assessment process. The interview included questions regarding sociodemographic characteristics (parental education and family annual income) and residential history. Ninety-eight per cent (471 out of 482) of families completed the telephone interview.

Data collection

Magnetic field exposure assessment Magnetic field exposure assessment was initiated after the child completed the initial

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induction therapy (usually 4 weeks from the start of therapy) and while the child was undergoing consolidation (intensification) therapy as an outpatient. The EMDEX Lite meter (Enertech Consultants Campbell, CA, USA), with pictorial and written instructions (English, Spanish, or French), was forwarded to families and returned by mail. Personal, 24-h MF exposures were monitored prospectively, with the first measurement taken shortly after enrolment and later measurements taken at the beginning of the second and third year after enrolment. The exposure protocol and results of demographic and serial MF exposure monitoring have been previously reported (Foliart *et al*, 2001, 2002).

A higher-than-expected percentage of families lost or never returned the meter (8%). Some families were reluctant to use the meter or had difficultly following the pictorial instructions, with 5% returning the meter with invalid or no data recorded. Based on follow-up telephone conversations with most of the 70 families who did not return valid first-year readings, it was clear that the diagnosis of leukaemia produced tremendous family stress and disruption, making it difficult to complete the exposure assessment protocol.

Completion of the exposure assessment protocol with return of viable data decreased during annual serial monitoring: 412 children completed the first monitoring, 304 completed a second measurement, and 134 completed a third measurement. The mean time-weighted average (TWA) (0.11 – 0.13 μT) and mean geometric mean (GM) (0.073 – 0.082 μT) were similar across the three measurement years (Foliart *et al*, 2002). Owing to the limited number of second- and third-year measurements, only the first year 24-h results were used in our analyses.

A priori, MF exposures were classified in a variety of ways, including TWA, GM, and two estimates of field stability: rate of change metric (RCM) and rate of change metric standardised (RCMS) (Burch *et al*, 1998). The metrics with the highest year-to-year correlation were TWA and GM. Rate of change metric and RCMS were poorly correlated over time (Foliart *et al*, 2002). Our final analyses used 24-h exposure classified by TWA and GM.

Clinical data At the time of diagnosis, all children had blood and bone marrow samples sent to a central reference laboratory at the University of Alabama, Birmingham, for cytogenetic analysis. For central assignment to their therapeutic regimen, children were stratified by immunophenotype and clinical prognostic factors by the POG Statistical Office at the University of Florida (Gainesville, FL, USA). For the commonest immunophenotype, B-precursor ALL, children were enrolled into one of three POG protocols based on prognostic factors at diagnosis predicting low, standard, or high risk of treatment failure (Borowitz *et al*, 1993). For children with B-precursor ALL enrolled before 2000 (330 out of 361 children), the National Cancer Institute (NCI) risk group criteria were used to determine the risk status, based on initial white blood cell count and age at diagnosis (Smith *et al*, 1996). In 2000, DNA Index and the presence of trisomies 4 and 10 were added to the risk stratification. While the criteria used to identify a child's risk were refined, children in a given risk stratum received similar treatment protocols over the course of the study. Protocols for T- and B-cell ALL did not change over the course of the enrolment period.

Data analysis

Of the 482 enrolled children, 412 (85%) completed the questionnaire and first-year MF assessment protocol and 386 (80%) were included in the analyses. The 26 ineligible children included 13 with missing data regarding response to induction therapy, 10 who did not enrol on a standardised treatment protocol, two with no follow-up data, and one whose diagnosis was later confirmed not to be ALL.

The primary outcome for this study was event-free survival, with additional analyses restricted to overall survival. Kaplan – Meier curves (Kaplan and Meier; 1958) with log rank tests (Peto *et al*, 1977) were used to examine the relationship between MF exposure (TWA <0.1, 0.1 – 0.19, 0.2 – 0.29, $>0.3\,\mu$T) and outcome. Event-free survival was defined as the interval of time from diagnosis to the date of last contact or to any of the following events that occurred: failure to attain a complete remission after induction therapy (Roberts *et al*, 1997), leukaemia relapse, secondary malignancy, or death from any cause. Removal for bone marrow transplantation was considered a censoring event (Pollock *et al*, 2000). Event-free survival was tracked through December 2004. Analyses were performed for all subjects combined and separately for B-precursor and T-cell ALL patients. Analysis of B-precursor ALL patients was adjusted by the NCI risk group criteria.

Multivariate analyses were conducted using Cox proportional hazards regression (Cox, 1972). The association between MF exposure and outcome, including analyses of trend across MF strata, as well as the association between other covariates and outcome, was estimated as the hazards ratio (HR) with 95% confidence interval (CI). Subjects with MF exposure $<0.1\,\mu$T constituted the reference group. Regression analyses were adjusted for a number of potential confounders and effect modifiers: NCI risk group, race/ethnicity, immunophenotype, and socioeconomic status (SES). Low SES was defined as annual family income <$40 000 and both parents with less than a college degree.

A number of other covariates were assessed in the secondary analyses. These included DNA Index, platelet count at diagnosis, presence of central nervous system involvement at diagnosis, trisomies 4 and 10, trisomy 21, trisomy 8, and several relatively rare cytogenetic translocations including t(9;22), t(4;11), and t(1;19). We examined the impact of these less common prognostic factors by individually adding them to a Cox regression model that included a primary MF exposure category and the NCI risk group.

Table 1 Race, ethnicity, and socioeconomic status of cohort[a]

		Socioeconomic status		Annual income		Maternal education		Paternal education	
	No. (%)	**High**	**Low**	**>$40 000**	**<$40 000**	**Some college**	**⩽High school**	**Some college**	**⩽High school**
White	290 (75)	239 (86)	39 (14)	150 (53)	132 (47)	196 (69)	88 (31)	182 (65)	98 (35)
African American	20 (5)	11 (73)	4 (27)	1 (5)	17 (94)	14 (74)	5 (26)	4 (27)	11 (73)
Hispanic	50 (13)	24 (56)	19 (44)	11 (22)	37 (77)	19 (39)	30 (61)	12 (27)	32 (73)
Native American	2 (0.5)	2 (100)	0	0	2 (100)	1 (50)	1 (50)	1 (50)	1 (50)
Asian	11 (3)	10 (100)	0	9 (90)	1 (10)	11 (100)	0	10 (91)	1 (9)
Hawaiian	9 (2)	6 (75)	2 (25)	3 (33)	6 (67)	5 (56)	4 (44)	4 (50)	4 (50)
Other	4 (1)	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)
Response missing	0	26		13		8		22	

[a]Per cent in parentheses, based on total with available information. A total of 386 families completed the telephone questionnaire, but answers to some queries were not known by respondents.

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RESULTS

Of the 386 children included in the analysis, 71% were less than 6 years old. Boys slightly outnumbered girls (52%). Table 1 presents details of race/ethnicity and SES. Most children (75%) were white; 41% were classified as having low SES. Annual family income, paternal education, and, to a lesser extent, maternal education varied widely by race and ethnic group (Table 1).

Most children completed the MF monitoring session shortly after diagnosis: 48% (186) within 2 months following diagnosis and 86% (332) within 4 months. The mean TWA was similar to that in other North American studies: 0.1 μT, with a 95th percentile value of 0.3 μT (Kaune and Zaffanella, 1994; Linet *et al*, 1997; Deadman *et al*, 1999).

Table 2 summarises the MF exposure findings. Only 19 children (5%) had a TWA $\geqslant$0.3 μT and 14 (4%) had a GM$\geqslant$0.3 μT. A higher percentage of non-white compared with white children (7.3 *vs* 4.1%) had TWA exposures $\geqslant$0.3 μT (odds ratio = 1.8, 95% CI 0.70, 4.77).

The median duration of follow-up among survivors was 5.07 years. There were 73 failure events among all children and 70 failure events among the 361 children with B-precursor ALL. There was a total of 30 deaths, of which 28 occurred among children with B-precursor ALL. In only one child was death the first failure event. For the 29 other children, the initial failure event was relapse ($n = 25$) or secondary malignancy ($n = 4$).

Table 2 Summary of 24-h time-weighted average (TWA) and geometric mean (GM) magnetic field exposure results

	TWA		GM	
Exposure (μT)	**Frequency**	**%**	**Frequency**	**%**
<0.1	251	65	294	76
0.1–0.19	95	25	67	17
0.2–0.29	21	5	11	3
0.3–0.39	7	2	10	3
0.4–0.49	7	2	4	1
0.5–0.59	1	0.3	0	0
$\geqslant$0.6	4	1	0	0
Total	386		386	

Figure 1 presents the Kaplan–Meier estimate of event-free survival for children with B-precursor ALL, stratified by 24-h TWA MF exposures (log rank test $P = 0.54$). Estimates using GM were similar and are not presented. Owing to small numbers, figures for total survival and T-cell ALL are not presented.

Cox proportional hazards regression analyses of survival are presented in Table 3. No statistically significant trend was noted between increasing exposure to MF and poorer event-free survival ($P = 0.5$). Five failures were observed among children exposed to $\geqslant$0.3 μT, four due to relapse and one due to secondary malignancy (four died during follow-up). Hazard ratios for children in the highest exposure category of $\geqslant$0.3 μT were increased in both univariate and multivariate analyses. In univariate analysis, the event-free survival HR for exposure $\geqslant$0.3 μT was 1.66, 95% CI 0.66, 4.18. Multivariate analyses of B-precursor ALL, adjusted for age at diagnosis and initial white blood cell count (NCI risk group) and SES, reported an HR for exposure $\geqslant$0.3 μT of 1.92, 95% CI 0.75, 4.90. Of the five failures in this exposure group, two occurred among the 11 white children and three occurred among the seven non-white children. Although failures were more common among non-white children, small numbers prevented us from adequately examining race-specific risks.

For overall survival, HRs were significantly elevated among children exposed to $\geqslant$0.3 μT in both univariate and multivariate analyses, based on four deaths (two in white children and two in non-white children). In univariate analysis, the HR was 3.39, 95%

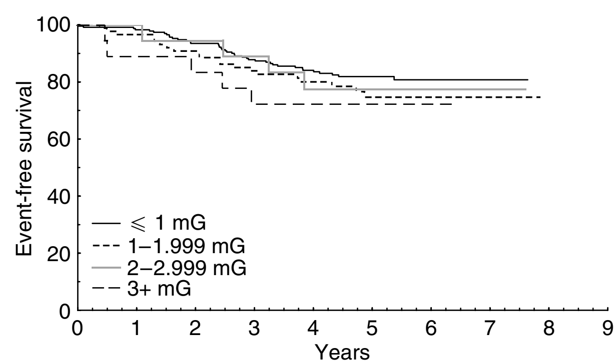

Figure 1 Kaplan–Meier estimates for event-free survival among children with B-precursor ALL, stratified by 24-h TWA MF exposure (log rank test $P = 0.054$).

Table 3 Association of magnetic field exposure and outcome: Cox proportional hazards regression analyses

	Event-free survival						Survival					
Variable	**No. of cases**	**No. failed[a]**	**HR**	**95% HR CI[b]**		**P[c]**	**No. of cases**	**No. failed**	**HR**	**95% HR CI**		**P[c]**
Univariate analysis	386	73				0.4	386	30				0.2
<0.1 μT	251	42	1.00				251	17	1.00			
0.1–0.19 μT	95	22	1.47	0.88	2.46		95	8	1.27	0.55	2.93	
0.2–0.29 μT	21	4	1.15	0.41	3.20		21	1	0.68	0.09	5.13	
$\geqslant$0.3 μT	19	5	1.66	0.66	4.18		19	4	3.39	1.14	10.06	
Multivariate analysis												
B-precursor[d]	361	70				0.5	361	28				0.06
NCI risk group			1.76	1.01	2.88				2.78	1.29	5.96	
SES			0.98	0.52	1.83				1.61	0.68	3.82	
<0.1 μT	235	41	1.00				235	16	1.00			
0.1–0.19 μT	89	20	1.25	0.72	2.19		89	7	1.16	0.47	2.84	
0.2–0.29 μT	19	4	1.32	0.47	3.71		19	1	0.85	0.11	6.40	
$\geqslant$0.3 μT	18	5	1.92	0.75	4.90		18	4	4.53	1.49	13.76	

[a]Failure events defined as failure to attain complete response during induction therapy, leukaemia relapse, secondary cancer, or death. [b]HR = hazard ratio; CI = confidence interval. [c]Test of trend for time-weighted average magnetic field exposure level. [d]Adjusted for National Cancer Institute (NCI) risk group and socioeconomic status (SES).

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CI 1.14, 10.06; in multivariate analysis, the HR was 4.53, 95% CI 1.49, 13.76. In the multivariate analysis, there was a marginal trend ($P = 0.06$) between increasing exposure category and deaths, although the number of deaths was small, with only one observed among the 19 children exposed to $\geqslant 0.2 - 0.29\,\mu$T.

As expected, children in the higher NCI risk group were at an increased risk of poor outcome for both event-free survival and total survival. Socioeconomic status was not associated with outcome. No significant first-order interaction terms were observed between MF exposure and the following covariates: DNA Index, platelet count at diagnosis, presence of central nervous system blast cells at diagnosis, and presence of translocations or trisomies (data not presented).

DISCUSSION

Although other studies have investigated MF exposure as a risk factor for incident ALL, this is the first study to address MF exposure and long-term survival among children with ALL. Strengths of the study include its prospective cohort design, use of centralised review of malignancy and biologic markers, inclusion of children from a wide geographic area, personal MF dosimetry, and the length and completeness of follow-up. Because failure events are most likely to occur within the first 5 years following diagnosis (Pollock *et al*, 2000), the study had an adequate duration of follow-up to capture most outcome events.

Three limitations of our study are noteworthy. As has been seen in earlier studies, only 5% of the cohort (19 children) had a TWA above $0.3\,\mu$T (Kaune and Zaffanella, 1994; Linet *et al*, 1997; Deadman *et al*, 1999). Thus, we had limited ability to evaluate outcome among children exposed to more than $0.3\,\mu$T and could perform no meaningful analyses above $0.4\,\mu$T. Secondly, less than one-third of potentially eligible children enrolled into our study, with lower participation rates among non-white children. The limited number of non-white children prevented meaningful multivariate analyses by racial/ethnic subgroups. Finally, our survival analyses were based on first-year MF exposure assessments. In an analysis of the subset of 304 children with two or more annual measurements, we found that first-year GM and TWA can serve as an estimate of exposure among residentially stable children (Foliart *et al*, 2002). However, a single measurement was less useful among children who changed residences. Twelve per cent of children with first-year measurements moved during the exposure assessment protocol. The total number of children who changed residences during the entire course of follow-up is unknown. The single assessment of MF exposure in residentially mobile children may not be an adequate surrogate of MF exposure over the study's extended follow-up period.

The focus of our study was the possible role of MF exposure as an independent predictor of event-free and overall survival. The number of failures was small: four among children exposed to $\geqslant 0.2 - 0.29\,\mu$T and five among children exposed to $\geqslant 0.3\,\mu$T. For overall survival, the HRs were significantly elevated among children exposed to $\geqslant 0.3\,\mu$T for both univariate and multivariate analyses. The multivariate HR (4.5) was based on only four deaths, yielding a wide CI (1.5, 13.8). No consistent or statistically significant trend was noted between increasing exposure to MF and event-free survival or risk of death. Although we report poorer survival among children with the highest MF exposure category, clinical inferences are limited, with results possibly attributable to chance alone. Independent confirmation is needed, as our study is the first to look at relapse and survival and thus our findings can be viewed only as hypothesis generating.

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CARPENTER DEPO
EXHIBIT 13

Acute low‐intensity microwave exposure increases DNA single‐strand breaks in rat brain cells

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Bioelectromagnetics

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Acute Low-Intensity Microwave Exposure Increases DNA Single-Strand Breaks in Rat Brain Cells

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Levels of DNA single-strand break were assayed in brain cells from rats acutely exposed to low-intensity 2450 MHz microwaves using an alkaline microgel electrophoresis method. Immediately after 2 h of exposure to pulsed (2 µs width, 500 pulses/s) microwaves, no significant effect was observed, whereas a dose rate-dependent [0.6 and 1.2 W/kg whole body specific absorption rate (SAR)] increase in DNA single-strand breaks was found in brain cells of rats at 4 h postexposure. Furthermore, in rats exposed for 2 h to continuous-wave 2450 MHz microwaves (SAR 1.2 W/kg), increases in brain cell DNA single-strand breaks were observed immediately as well as at 4 h postexposure.

Key words: microwaves, brain cells, DNA damage, rats, single-strand

INTRODUCTION

In this paper, we report the results from an experiment to study the effect of acute exposure to low-intensity microwaves on DNA damage in brain cells of the rat. Well-characterized damages to DNA include DNA single and double strand breaks, alkali labile sites (apurinic, apyrimidinic, alkylation, and phosphotriester formation), base damage, base modification, DNA-DNA and DNA-protein cross links, pymidine dimers, and DNA adducts. Among all of these, the most commonly used marker for DNA damage is single-strand break. DNA single-strand breaks can lead to carcinogenicity [Tice, 1978; Cerutti, 1985; Ames, 1989a,b], cell death [Walker et al., 1991; Onishi et al., 1993; Prigent et al., 1993], and aging [Hart and Setlow, 1974; Tice, 1978]. We used the alkaline microgel electrophoresis method [Singh et al., 1988, 1991, 1994] to assay for DNA single-strand breaks in individual brain cells. This is the most sensitive method available for assaying DNA single-strand breaks and can detect one break per 2×10^{10} daltons of DNA in lymphocytes.

MATERIALS AND METHODS

Male Sprague-Dawley rats (250–300 g) purchased from B and K Laboratory (Bellevue, WA) were used in this research. They were housed three in a cage in a vivarium on a 12 h light-dark cycle (light on 7 AM to 7 PM) at an ambient temperature of 22 °C and a relative humidity of 65%. They were given food and water ad libitum.

The cylindrical waveguide system developed by Guy et al. [1979] was used for microwave exposure. Our waveguide system consists of eight individual cylindrical exposure tubes connected though a power-divider network to a single microwave power source. Each tube consists of a section of circular waveguide constructed of galvanized wire screen in which a circularly polarized TE_{11} mode field configuration is excited. The tube also contains a plastic chamber to house a rat. This waveguide system, using circularly polarized radiation, enables efficient coupling of microwave energy to the animal exposed. For example, a spatially averaged power density of 1 mW/cm² in the waveguide produces a whole body specific absorption rate (SAR) of 0.6 W/kg in the rat. The range of power densities for a linearly polarized plane wave associated with an SAR of 0.6 W/kg would approximate 3–6 mW/cm². Local SAR in eight brain regions measured in rats exposed in this waveguide

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system varied from 0.5 to 2.0 W/kg per mW/cm² [Chou et al., 1985]. With this system, rats can be irradiated with either continuous-wave (CW) or pulsed (2 μs pulses, 500 pps) 2450 MHz microwaves at different spatially averaged power densities.

In our experiments, animals were subjected to either microwave or sham exposure in the waveguide system for 2 h. Immediately or at 4 h after exposure, rats were placed in a closed box containing dry ice for 60 s and then decapitated. All procedures from this time onward were done in minimum light. Brains were removed immediately and dissected on ice for assay of DNA single-strand breaks. Removal of the brain from the skull took approximately 30 s, and dissection of the hippocampus took an additional 40–45 s. All experiments were run blind. Two workers were involved: One conducted the animal exposure and brain dissection, and the other conducted the DNA single-strand break assay. Neither worker knew the treatment condition (microwave or sham exposed) of the rats.

The method of Singh et al. [1994] was used to assay for DNA single-strand breaks in brain cells with minor modifications. All chemicals used in the assay were purchased from Sigma Chemical Co. (St. Louis, MO) unless otherwise noted. Immediately after dissection, brain tissues were immersed in ice-cold phosphate-buffered saline (PBS; NaCl, 8.01 g; KCl, 0.20 g; Na_2HPO_4, 1.15 g; KH_2PO_4, 0.20 g per liter) with 200 μM N-t-butyl-α-phenylnitrone at pH 7.4. Tissue was washed four times with the same buffer to remove most of the red blood cells. A pair of sharp scissors was used to mince (approximately 200 times) the tissue in a 50 ml polypropylene centrifuge tube containing 5 ml of ice-cold PBS to obtain pieces of approximately 1 mm³. Four more washings with the cold buffer removed most of the remaining red blood cells. Finally, in 5 ml of PBS, these tissue pieces were dispersed into single-cell suspension using a 5000 liter Pipetman. Therefore, this cell suspension consisted of different types of cells in the brain.

A small volume (10 μl) of this cell suspension was mixed with 0.2 ml of 0.5% agarose maintained at 37 °C, and 75 μl of this mixture was pipetted onto a fully frosted slide (Erie Scientific Co., Portsmouth, NH) and immediately covered with a 24 × 50 mm² No. 1 coverglass (Corning Glass Works, Corning, NY) to make a microgel on the slide. Slides were put in an ice-cold steel tray on ice for 1 min to allow the agarose to gel. The coverglass was removed, and 75 μl of agarose solution was layered as before. This layering was done very quickly, because agarose solidifies rapidly on top of a cold agarose layer.

Slides were then immersed in an ice-cold lysing solution (2.5 M NaCl, 1% sodium N-lauroyl sacosinate, 100 mM disodium EDTA, 10 mM Tris base, and 1% Triton-X 100, pH 10). After 1 h of lysing at 0 °C, slides were treated with DNAase-free proteinase K (Boehringer Mannheim Corp., Indianapolis, IN) in lysing solution for 2 h at 37 °C. The proteinase K solution was preincubated for 1 h at 37 °C to ensure DNAase inactivation. Slides were then put on the horizontal slab of an electrophoretic assembly (Hoefer Scientific, San Francisco, CA) modified so that both ends of each electrode are connected to the power supply. Nine hundred milliliters of an electrophoretic buffer (300 mM NaOH, 0.1% 8-hydroxyquinoline, 2% dimethyl sulfoxide, and 10 mM tetrasodium EDTA) were gently poured into the assembly to cover the slides to a height of 6 mm above their surface.

After 20 min to allow for DNA unwinding, electrophoresis was started (18 V, approximately 300 mA, for 60 min), and the buffer was recirculated at a rate of 100 ml/min. At the end of the electrophoresis, extra electrophoretic buffer was removed from the top of the slides. The slides were gently removed from the electrophoretic apparatus and immersed for neutralization in 35 ml of 0.4 M Tris, pH 7.4, in a Coplin jar (two slides per jar) for 30 min. After two more similar steps of neutralization, the slides were dehydrated in absolute ethanol in a Coplin jar three times for 30 min and blow dried. One slide at a time was taken out and stained with 50 μl of 1 μM solution of YOYO-1 (stock, 1 mM in DMSO from Molecular Probes, Eugene, OR) and then covered with a 24 × 50 mm coverglass.

Slides were examined and analyzed with a Reichert vertical fluorescent microscope (model 2071) equipped with a filter combination for fluorescence isothiocyanate (excitation at 490 nm, emission filter at 515 nm, and dichromic filter at 500 nm). We measured the length (in microns) from the beginning of the nuclear area to the last pixel of DNA at the leading edge. The migration length is used as the index of DNA single-strand breaks. (As a reference, lymphocytes exposed to 25 rads of X-rays show an increase of 50–60 μm of DNA migration when assayed with this method.) Fifty representative cells were measured per slide. Data were analyzed by ANOVA, and difference between groups was compared by the Newman- Keuls test. A difference at $P < .05$ was considered statistically significant.

RESULTS

In the first experiment, we exposed rats for 2 h to 2450 MHz pulsed (2 μs pulses, 500 pps) microwaves at spatially averaged power density of either 1 or 2 mW/cm² inside the waveguide. These power densities give an average whole-body SAR of 0.6 and 1.2 W/kg, respectively, in the exposed animals [Chou et al., 1984]. Amounts of DNA single-strand breaks in cells from the hippocampus and the rest of the brain were assayed

immediately and at 4 h postexposure. Figures 1 and 2 show an increase in DNA single-strand breaks (expressed as microns of migration) in cells of the hippocampus and the rest of the brain, respectively, of the microwave-exposed rats at 4 h after exposure (Figs. 1, 2; right), whereas no significant effect was seen immediately after 2 h of microwave exposure (Figs. 1, 2; left).

In a second experiment, the effect of CW microwave radiation was investigated. Rats were exposed to CW 2450 MHz microwaves for 2 h in the circular waveguide at a power density of 2 mW/cm^2 (average whole-body SAR of 1.2 W/kg). DNA single-strand breaks were assayed in cells obtained from the whole brain of the animals immediately and at 4 h postexposure. Data in Figure 3 show a significant increase in DNA single-strand breaks in brain cells of the microwave-exposed rats compared to those of sham-exposed animals. Increase in breaks was observed immediately after microwave exposure and at 4 h postexposure. It should be noted that the baseline of DNA single-strand breaks in the sham-exposed samples in this experiment is lower than that in the previous experiment. This difference could be due to the use of whole brain in this study, whereas, in the previous study, the hippocampus was dissected out and assayed separately from the rest of the brain. The dissection process took 40–45 s more before the tissues could be put into ice-cold buffer for processing. Such a delay and the additional disturbance to the tissue during dissection could increase the baseline level of DNA breaks.

DISCUSSION

Our data indicate that acute microwave exposure increases DNA single-strand breaks in brain cells of the rat. Previous studies have also suggested effects of microwave exposure on chromosome and DNA. Garaj-Vrhovac et al. [1991] showed that acute (15–60 min) exposure to 7.7 GHz microwaves at 0.5 mW/cm^2 caused higher incidence of chromosome aberrations in Chinese hamster fibroblasts. Maes et al. [1993] reported that acute exposure to 2450 MHz microwaves at SAR of 75 W/kg and constant temperature increased dicentric chromosome and acentric chromosomal fragments in human lymphocytes. Both studies suggest damage of chromosomal DNA in cells after microwave exposure. In an in

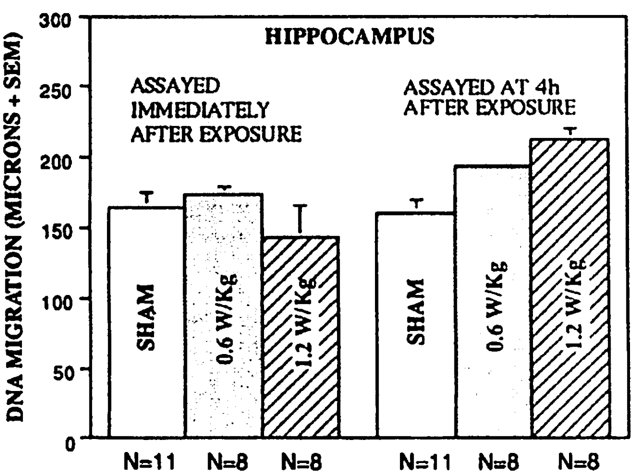

Fig. 1. DNA single-strand breaks (shown as micrometers of migration during electrophoresis) in hippocampal cells of rats subjected to 2 h of exposure to pulsed microwaves at an average whole-body SAR of 0.6 or 1.2 W/kg or sham exposure. Assay was done immediately after exposure (**left**) or at 4 h postexposure (**right**). N is the number of rats studied. One-way ANOVA showed no significant treatment (microwave) effect on DNA migration immediately after exposure ($F[2,24] = 1.239$; nonsignificant), whereas a significant treatment effect was observed at 4 h postexposure ($F[2,25] = 12.22$; $P < .001$). Values of 0.6 and 1.2 W/kg are significantly different from sham exposure at $P < .01$ (Newman-Keuls test). No significant difference was found between exposures at 0.6 and 1.2 W/kg.

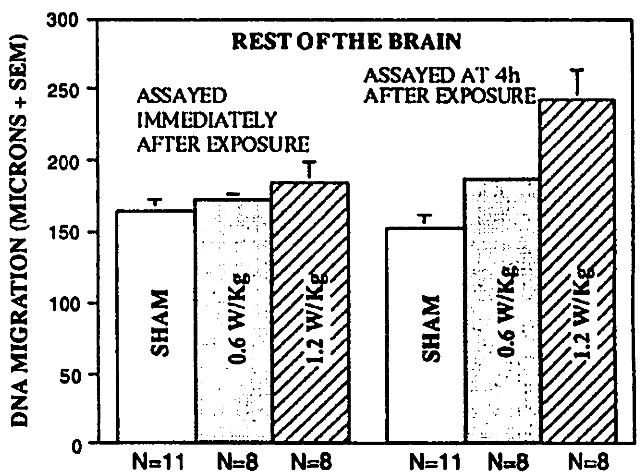

Fig. 2. DNA single-strand breaks (shown as micrometers of migration during electrophoresis) in cells from the rest of the brain (i.e., whole brain minus hippocampus) of rats subjected to 2 h of exposure to pulsed microwaves at an average whole body SAR of 0.6 or 1.2 W/kg or sham exposure. N is the number of rats studied. Assay was done immediately after exposure (**left**) or at 4 h postexposure (**right**). One-way ANOVA showed no significant treatment (microwave) effect on DNA migration immediately after exposure ($F[2,24] = 1.288$; nonsignificant), whereas a significant treatment effect was observed at 4 h postexposure ($F[2,24] = 14.04$; $P < .001$). Values of 0.6 and 1.2 W/kg are significantly different from sham exposure at $P < .05$ and .01 (Newman-Keuls test), respectively. A significant difference at $P < .01$ was found between exposures at 0.6 and 1.2 W/kg.

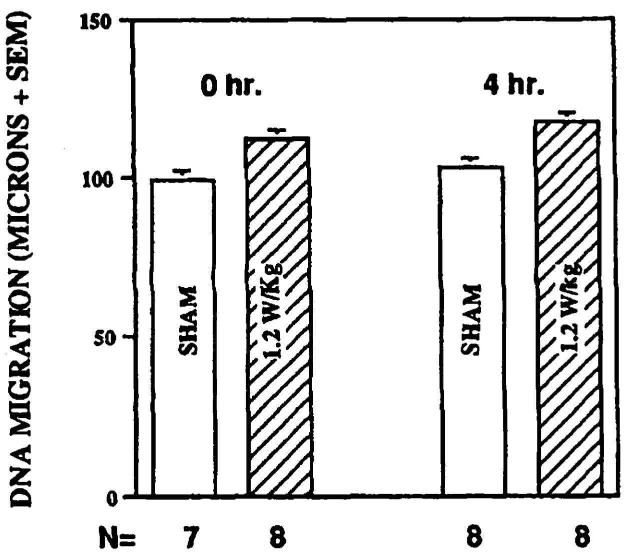

Fig. 3. Effect of acute exposure (2 h) to continuous-wave 2,450 MHz microwaves (SAR 1.2 W/kg) on DNA single-strand breaks in cells of the rat brain. Brain cells from microwave- and sham-exposed rats were assayed immediately and at 4 h postexposure. Two-way ANOVA showed a significant effect of microwaves ($F[1,27] = 25.18$, $P < .005$). Differences between microwave- and sham-exposed rats were significant at $P < .01$, both immediately and at 4 h after exposure, when compared using the Newman-Keuls test. There is no significant effect due to time of assay ($F[1,27] = 1.79$; nonsignificant) nor time of assay × microwave interaction effect ($F[1,27] = 1.582$; nonsignificant).

vitro study, Sagripanti and Swicord [1986] reported an increase in single- and double-strand breaks in isolated DNA after acute microwave exposure. Recently, Sarkar et al. [1994] reported a change in the sizes of DNA fragments isolated from the brain and testis of mice given repeated exposure to 2450 MHz microwaves at 1 mW/cm² (SAR 1.18 W/kg).

The mechanism of interaction between microwaves and DNA is unknown. An increase in DNA single-strand breaks could be due to an increase in the rate of breaking or a reduction in the DNA damage repair processes in the cell. It is also puzzling that brain cell DNA responded differently to CW and pulsed microwaves. A significant increase in DNA single-strand breaks was observed immediately after exposure to CW but not to pulsed microwaves. This further supports our previous conclusion that biological responses to microwaves depend on the parameters of the radiation [Lai, 1992].

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Exposure to Magnetic Fields and Survival after Diagnosis of Childhood Leukemia: A German Cohort Study

CARPENTER DEPO EXHIBIT 14

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Abstract

Inspired by a recent U.S. study showing poorer survival among children with acute lymphoblastic leukemia (ALL) exposed to magnetic fields above 0.3 μT, we examine this relationship in a German cohort of childhood leukemia cases derived from previous population-based case-control studies conducted between 1992 and 2001. A total of 595 ALL cases with 24-h magnetic field measurements are included in the analysis with a median follow-up of 9.5 years. We calculate the hazard ratios (HR) using the Cox proportional hazards model for overall survival, adjusted for age at diagnosis, calendar year of diagnosis, and gender. Elevated hazards are found for exposures between 0.1 and 0.2 μT [HR, 2.6; 95% confidence interval (95% CI), 1.3-5.2], based on 34 cases with 9 deaths as well as for exposures above 0.2 μT (HR, 1.6; 95% CI, 0.6-4.4), based on 18 cases with 4 deaths. After adjustment for prognostic risk group, the hazard for exposures above 0.2 μT increases to HR, 3.0 (95% CI, 0.9-9.8). In conclusion, this study is generally consistent with the previous finding; however, we report the excess risk at field levels lower than those in the U.S. study. In all, the evidence is still based on small numbers, and a biological mechanism to explain the findings is not known. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1167–71)

Introduction

The relation between exposure to extremely low-frequency magnetic fields and the risk of childhood leukemia has been examined in several studies. Most epidemiologic studies have shown a small increase in risk with higher exposures (above 0.3 or 0.4 μT; ref. 1), but the overall evidence is still inconclusive because the association found in observational studies lacks both a plausible mechanism and supportive evidence from experimental studies (2). Recently, this was taken a step further by Foliart et al. (3); if exposure to magnetic fields is associated with increased leukemia incidence, it could also have a relationship with survival. Indeed, they reported a somewhat poorer survival among 412 U.S. childhood acute lymphoblastic leukemia (ALL) patients exposed to magnetic fields above 0.3 μT compared with those exposed to magnetic fields below 0.1 μT. However, due to small numbers of exposed children, the authors themselves characterized their study as only hypothesis generating. Here, we investigate this new hypothesis in a German cohort of 595 childhood ALL patients.

Materials and Methods

We use data on childhood leukemia and extremely low-frequency (ELF) magnetic fields from three different studies conducted previously in Germany (Table 1; refs. 4-6). They were all population-based case-control studies, with the cases identified through the German Childhood Cancer Registry (GCCR), which is estimated to be more than 95% complete (7). The cohort consisted of children <15 years old who were living in the relevant study area (see below) at the date of diagnosis. Magnetic field exposure levels were assessed by 24-h measurements taken within each child's bedroom, and additional information on other risk factors or potential confounders was obtained from questionnaires. The first study covered Lower Saxony (northwestern part of Germany; population, 7.4 million) with children diagnosed during the period July 1988 to June 1993, and measurements done between November 1992 and July 1995 (4). The second study was conducted in Berlin and included children diagnosed between January 1991 and September 1994, with measurements done between November 1992 and mid-1996 (5). The third study covered the whole of former West Germany with children diagnosed between October 1992 and September 1994, plus an extra component of children living in the vicinity of German nuclear installations and diagnosed between January 1990 and September 1994. The measurements were done between November 1997 and December 1999 (6). A few children were eligible for more than one study. But once included in one study, the children were not included in any of the following studies. The response rates in the three studies varied from 59% to 66% of eligible children. The numbers of ALL cases contributed from each study are 108 (Lower Saxony), 38 (Berlin), and 449 (West Germany), for a total of 595 children.

Over 98% of German children with leukemia are treated in clinical trials. Follow-up of the patients established at the GCCR can be described as follows: during the first 5 years after the end of treatment, the GCCR receives follow-up information about the children from the clinical trial centers once a year. In a second phase, the GCCR asks the respective hospitals for information every 3 years. When the children are grown up and no longer connected to the pediatric hospitals, they are actively followed up by the GCCR by mail every 5 years for their entire lifetime. By all three mechanisms, the exact dates of an event (death, relapse, and secondary tumor) are obtained. In case no event occurred, the date of the last contact is recorded. For more details, see Kaatsch et al. (8). Effective February 2006, the longest follow-up was 16.4 years, and the median was 9.5 years.

To adjust for the stage of the disease, the cases are classified by prognostic risk groups, which was possible for children treated within the major clinical trials. Most German children with ALL are treated in the ALL-BFM (Berlin, Frankfurt, Münster) trials, which were initiated in 1976. The consecutive trials ALL-BFM 86 and ALL-BFM 90 recruited patients

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Table 1. Overview of the three original studies

Study	Lower Saxony	Berlin	West Germany
Children diagnosed between	July 1988 to June 1993	January 1991 to September 1994	January 1990 to September 1994
Measurements done between	November 1992 to July 1995	November 1992 to July 1996	November 1997 to December 1999
Number of children	108	38	449
Person-years of follow-up	1,160	299	3,953
Number of children with prognostic risk group	88	37	361
Children in standard-risk group	23	7	105
Children in medium-risk group	56	29	218
Children in high-risk group	9	1	38

between October 1986 and March 1995 (9, 10). Briefly, risk groups were divided into three categories. The standard-risk group had to fulfill all of the following six criteria: (*a*) a low score (<0.8) composed of absolute peripheral blast cells; (*b*) liver size and spleen size (calculated 0.2 × log(blasts+1) + 0.06 × liver size + 0.04 × spleen size); (*c*) a peripheral blast count <1 G/L on day 8 after 1 week of prednisone therapy; (*d*) CR in the bone marrow on day 33 (<5% blasts in the bone marrow after regeneration with normal or nearly normal cellularity); (*e*) neither mediastinal tumor nor pre−T-/or T-immunology (TdT^+, $CyCD3^+$, $CD7^+$; ref. 10); (*f*) no evidence of central nervous system involvement and no *t*(9;22) or BCR-ABL recombination. The median-risk group contained four items that had to be fulfilled: (*a*) a higher score as mentioned above (≥0.8); (*b*) peripheral blast count <1 G/L on day 8 after 1 week of prednisone therapy; (*c*) CR in the bone marrow on day 33; (*d*) no *t*(9;22) or BCR-ABL recombination. The high-risk group was characterized by one of the following: blast count more than 1 G/L on day 8 after 1 week of prednisone, *t*(9;22) or BCR-ABL, or no CR on day 33.

The information on risk groups is unfortunately only available from some hospitals. Thus, analyses including risk groups further restrict the sample to 88, 37, and 361 cases from Lower Saxony, Berlin, and West Germany, respectively, with a total of 486 cases of ALL (Table 1).

The relation between exposure to ELF magnetic fields and overall survival after the diagnosis of ALL was assessed using the Cox proportional hazards model adjusting for age, calendar year at diagnosis, and gender. Season of measurement, socioeconomic status (average or high), and type of residential area (rural, mixed, or urban) were examined as additional potential confounders but were not included in the final model. Cases were followed from the date of diagnosis until date of death (=event), and those alive at the end of the study period were censored at day of last contact. Analyses were conducted for the full cohort and for the sample with prognostic data stratified by risk group. As in our previous studies (4-6), the exposure metric was the median magnetic field of the 24-h bedroom measurement which was divided into three exposure categories: low, below 0.1 μT; medium, from 0.1 to 0.2 μT; and high, above 0.2 μT.

In addition, the study by Foliart et al. (3) was replicated as close as possible; we excluded children below 1 year of age and children who were not in remission and used the exposure groups <0.1, 0.1 to 0.2, 0.2 to 0.3, and above 0.3 μT. For this approach, both an overall survival analysis and an event-free survival analysis (where death, relapse, and secondary tumor are considered events and cases were followed until the respective date of the first event or censored at day of last contact) with the same adjustment as above were done.

Results

Exposure and prognostic risk group did not seem to be associated, consistent with Foliart et al. (ref. 11; Table 2). The Kaplan-Meier survival curve showed clear differences among the three magnetic field exposure groups (Fig. 1). For these unadjusted data, the survival was slightly better for the high exposed than for the medium exposed.

In the course of developing the analytic model for the adjusted risk estimates, the effect of the potential confounding factors (age at diagnosis, year of diagnosis, gender, socioeconomic status, type of residential area, season of measurement) was assessed in an overall survival analysis restricted to the low-exposure group only (<0.1 μT). The effect of age was modeled as a spline; the hazard decreased rather steeply up until the age of 3 years, with hazard ratios (HR) of 0.6 [95% confidence interval (95% CI), 0.4-1.0] per year, and from there on, it increased slightly, HR, 1.1 (95% CI, 1.0-1.2) per year. Year of diagnosis was included as a linear variable, and there was some decrease in hazard over time, HR, 0.9 (95% CI, 0.8-1.1) per year. Gender showed a tendency with girls having a better survival than boys, HR, 0.6 (95% CI, 0.3-1.1). Neither socioeconomic status, type of residential area, or season of measurement had a relevant impact. Consequently, age, calendar year of diagnosis, and gender were included in the main analyses.

The adjusted results are shown in Table 3. For the subcohort with stratification for risk group, the respective HRs were 2.8 (95% CI, 1.2-6.2) for medium and 3.0 (95% CI, 0.9-9.8) for high exposure based on 7 and 3 deaths, respectively. For a trend analysis using magnetic field as a continuous variable, the estimated HR was 1.4 (95% CI, 1.0-1.8) per 0.1-μT increment (Table 2); in this analysis with exposure as a continuous variable, any measurement below 0.1 μT was set to be 0.05 μT because this was considered a reasonable detection limit.

For the entire cohort without stratification, we computed adjusted HRs of 2.6 (95% CI, 1.3-5.2) for the medium-exposure group and 1.6 (95% CI, 0.6-4.4) for the high-exposure group, whereas the HRs for the subcohort without stratification were 2.4 (95% CI, 1.1-5.2) and 2.1 (95% CI, 0.7-7.0) for the medium- and high-exposure groups, respectively.

The replication of Foliart's analytic model (3) included a total of 460 cases and resulted in HRs for overall survival of 3.1 (95% CI, 1.3-7.3), 2.7 (95% CI, 0.4-20.2), and 2.8 (95% CI, 0.4-20.6) for the exposure groups 0.1 to 0.2, 0.2 to 0.3, and above 0.3 μT, respectively, based on 6, 1, and 1 deaths. For the event-free survival, the corresponding HRs were 2.2 (95% CI, 1.0-4.5), 1.5 (95% CI, 0.2-11.2), and 1.4 (95% CI, 0.2-9.9) based on 8, 1, and 1 events.

Table 2. Relation between prognostic risk group and exposure

Risk group	Exposure		
	Low, <0.1 μT	Medium, 0.1 to <0.2 μT	High, ≥0.2 μT
Standard	122	10	3
Medium	277	17	9
High	46	2	0

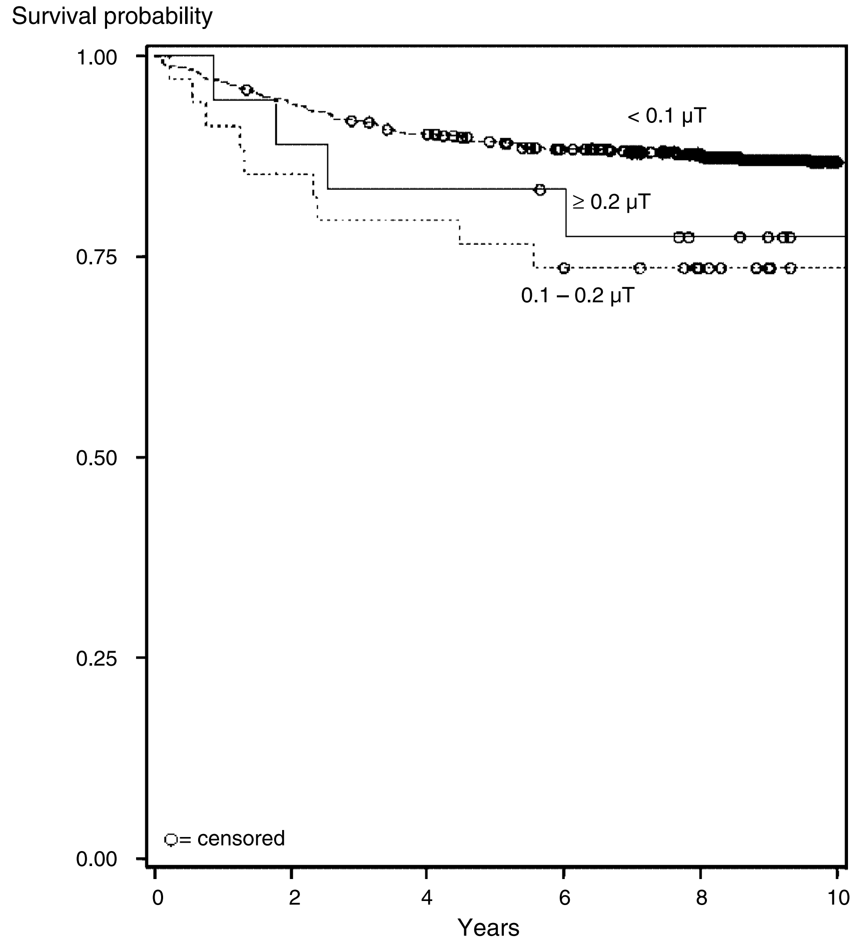

Figure 1. Survival distribution as a function of years since diagnosis for the three groups of exposure to magnetic fields separately.

Discussion

Our main finding is an elevated risk of survival failure among childhood ALL cases in the medium (0.1-0.2 µT) and high (>0.2 µT) magnetic field exposure groups. With stratification for prognostic risk group, the highest risk appears for the highest exposure group, whereas without stratification, it appears for the medium-exposure group. Thus, there is a tendency for the HRs to increase with increasing exposure, although it does not seem to be linear. Being the predictor of survival, the stratification for prognostic risk group is justified though it reduces the data material, and to illustrate the effect of excluding subjects with unknown risk group, we present the unadjusted HRs for both the full cohort and the subcohort.

A similar trend was reported by Foliart et al. (3), but they only reported increased survival failure for cases classified with magnetic field levels above 0.3 µT; in our study, excess risk appears with exposure levels above 0.1 µT. Apart from differences in the assessment of exposure, the main differences between the studies concern participation rate and duration of follow-up. The study by Foliart had a 29% participation rate, with the lowest rate among non-White children. Moreover, a higher percentage of non-White children than of White children were classified with high exposure. Thus, in their study population, the high exposed (non-White) children may have been underrepresented, thereby decreasing the power of the study. In our study with the median follow-up of 9.5 years, 83% of the failure events happened within the first 5 years after diagnosis, which can also be seen from Fig. 1. The Foliart study had a median follow-up of 5.07 years, so they might have missed some failure events if their data had been similar to ours, which could affect the result in either direction. The prognostic risk groupings also differ as to how they are defined in the German and U.S. ALL clinical trials. Foliart et al.'s (3) primary exposure metric was the mean personal field level logged over a 24-h period in the weeks following enrollment. Our study used the median 24-h bedroom measurement within a few years after diagnosis. In the Foliart study, the families did the measurements themselves according to the protocol received from the investigators, whereas in our study, they were done by professionals according to a standardized protocol.

Our finding of improved survival over time for year of diagnosis is well in accordance with the existing literature (12). As for the dependence on age, it is known that the very young (below 1 year of age) and the group aged 10 to 14 have the poorest survival, but other than that, survival is only considered by 5-year age groups (12). Making the reasonable assumption that age-specific survival is a smooth curve, this still offers support for our finding of the simplified spline with the knot at age 3 years. The poorer survival of boys than of girls, although not significant, is also in agreement with findings in previous survival studies (12). These findings support the validity of our statistical model and the representativeness of our study population.

As an alternative to follow the children from date of diagnosis, we also did similar analysis following the ones who reached remission from that point forward. The results did not change (data not shown).

In this study, we had a participation rate of ~60%, and this could introduce a bias. It could be that mainly the ones living beneath power lines (and who are worried about this) choose to participate. This would result in a larger proportion of our study group being in the high-exposure group, and having many highly exposed would only increase the power of the study but not introduce a bias. Another concern could be that

Table 3. Association of magnetic field exposure and childhood leukemia survival

Exposure	Cases	Events	Person-years	HR† with CI
Subgroup*				
With stratification for risk group				
Total	486	65	4,356	
<0.1 μT	445	55	4,016	1
0.1 to <0.2 μT	29	7	247	2.8 (1.2-6.2)
≥0.2 μT	12	3	93	3.0 (0.9-9.8)
Continuous,‡ HR per 0.1 μT				1.4 (1.0-1.8)
Subgroup*				
No stratification for risk group				
Total	486	65	4,356	
<0.1 μT	445	55	4,016	1
0.1 to <0.2 μT	29	7	247	2.4 (1.1-5.2)
≥0.2 μT	12	3	93	2.1 (0.7-7.0)
Total cohort*				
No stratification for risk group				
Total	595	83	5,412	
<0.1 μT	543	70	4,978	1
0.1 to <0.2 μT	34	9	281	2.6(1.3-5.2)
≥0.2 μT	18	4	154	1.6(0.6-4.4)

*Subgroup is all subjects of the total cohort, for whom information on prognostic risk group was available.
† Hazard ratios from Cox proportional hazards model with adjustment for age at diagnosis, calendar year of diagnosis, and gender, with and without stratification by risk group.
‡ In the continuous analysis, any exposure below 0.1 μT was set to be 0.05 μT because we consider this to be a reasonable detection limit of an accurate measurement.

low social class patients have both poorer survival and higher exposures. We do not believe that this is a great concern for the German study, due to the German health care system of free and equal access, and also supported by the observation that adjusting for socioeconomic status had no impact on the results. It could also be reasonable to expect that the degree of illness of the child influences participation. A proxy for this is prognostic risk group. As shown in Table 1, the distribution of risk groups is similar for all three exposure categories. One word of warning, however, is that this is based on small numbers. The largest group (the low-exposure group) is distributed with 27% of patients in the standard-risk group, 62% in the medium-risk group, and 10% in the high-risk group. This is well in line with the distribution found in a large clinical trial (n = 2,178; ref. 10), where the same groups contain, respectively, 29%, 60%, and 11%, offering support to the viewpoint that there is no selection bias. Other strengths of the study are that the exposure assessment is based on objective measurements, and that the follow-up is long enough as can be seen from the Kaplan-Meier curve (Fig. 1).

A weakness of our study is that the study material was collected for another purpose than the analyses presented here. This in particular means that the measurement of magnetic fields was done after diagnosis, but in the house where the child lived longest before diagnosis. Thus, the exposure could have been assessed in a house where the child no longer lived. For 75% of our cohort, we had information about mobility before diagnosis. Out of these children, 96% had lived in the same place a year before diagnosis, as where the measurements were later done. Thus, the study population is not very mobile, so for most children, the exposure was assessed in the residence where they also lived after diagnosis. Some misclassification cannot be ruled out, but there is no reason to believe that it would be differential. Even in the case where one child who died from leukemia was wrongly placed in the medium exposure group instead of in the reference group, this would only change the HR for the medium-exposure group to a value between 2.3 and 2.6, depending on which one of the events was misclassified. So although the number of events in the medium category is low, the unlikely event of one of these events being misclassified does not explain our findings. Another weakness is that we consider overall survival, instead of leukemia-specific survival, but the cause of death is not systematically recorded in the clinical trial databases. However, given that our cohort consist of (German) children, any other cause of death is not likely, and out of 82 patients for whom cause of death was recorded, only one had a cause of death not related to the disease. A competing cause of death is death from a secondary tumor. It could obviously be debated how these deaths should be treated because most likely, they are treatment related. They are included in our analysis because our outcome of primary interest is overall survival. But only seven children, all in the reference group, have a secondary tumor. Four of these children died during the follow-up period. If they were excluded from the analysis, this would increase the HRs. The seven deaths in the medium exposure category occurred between the age of 4 and 14 years. Even if one of these deaths was not due to leukemia, then this would only change the result to a HR between 2.3 and 2.4 for the medium-exposure group, depending on which one of the seven deaths it was.

After adjusting for confounders, we observed elevated HRs of survival from childhood ALL associated with exposure to magnetic fields. Selection bias is likely to be a minor problem compared with previous case-control studies that have addressed the association of leukemia with magnetic fields (1). There is at present no biological explanation as to how exposure to magnetic fields could increase the risk of leukemia. However, if this is the case, exposure to magnetic fields might also increase the risk of relapse or failure of treatment and thereby decrease survival. However, in our study and in the previous one (3), the association between survival failure and magnetic fields was stronger in the overall survival analysis than in the event-free survival analysis. Possible explanations could be that exposure to magnetic fields has a higher impact on the risk of death than on the risk of relapse, that exposure to magnetic fields shortens the time from relapse to death, or that it is just a reflection of random variation due to small numbers.

In conclusion this study's results are broadly consistent with Foliart et al. (3) in that poorer survival among childhood ALL patients occurred in children in the higher exposure categories. However, the HRs here were seen at lower field levels than in the U.S. study. In all, the evidence is still based on small numbers, and a biological mechanism to explain the findings is not known.

Acknowledgments

We thank the ALL-BFM study group with Prof. M. Schrappe as principal investigator.

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Exposure to Magnetic Fields and Survival after Diagnosis of Childhood Leukemia: A German Cohort Study

Anne Louise Svendsen, Thomas Weihkopf, Peter Kaatsch, et al.

Cancer Epidemiol Biomarkers Prev 2007;16:1167-1171.

CARPENTER DEPO EXHIBIT 15

Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposures)

Draft 2-1-2018

Table of Contents

Abstract

The U.S. National Toxicology Program (NTP) has carried out extensive rodent toxicology and carcinogenesis studies of radiofrequency radiation (RFR) at frequencies and modulations used in the U.S. telecommunications industry. This report presents partial findings from these studies. The occurrences of two tumor types in male Harlan Sprague Dawley rats exposed to RFR, malignant gliomas in the brain and schwannomas of the heart, were considered of particular interest and are the subject of this report. The findings in this report were reviewed by expert peer reviewers selected by the NTP and National Institutes of Health (NIH). These reviews and responses to comments are included as appendices to this report, and revisions to the current document have incorporated and addressed these comments. When the studies are completed, they will undergo additional peer review before publication in full as part of the NTP's Toxicology and Carcinogenesis Technical Reports Series. No portion of this work has been submitted for publication in a scientific journal. Supplemental information in the form of four additional manuscripts has or will soon be submitted for publication. These manuscripts describe in detail the designs and performance of the RFR exposure system, the dosimetry of RFR exposures in rats and mice, the results to a series of pilot studies establishing the ability of the animals to thermoregulate during RFR exposures, and studies of DNA damage. (1) Capstick M, Kuster N, Kühn S, Berdinas-Torres V, Wilson P, Ladbury J, Koepke G, McCormick D, Gauger J, and Melnick R. A radio frequency radiation reverberation chamber exposure system for rodents; (2) Yijian G, Capstick M, McCormick D, Gauger J, Horn T, Wilson P, Melnick RL, and Kuster N. Life time dosimetric assessment for mice and rats exposed to cell phone radiation; (3) Wyde ME, Horn TL, Capstick M, Ladbury J, Koepke G, Wilson P, Stout MD, Kuster N, Melnick R, Bucher JR, and McCormick D. Pilot studies of the National Toxicology Program's

cell phone radiofrequency radiation reverberation chamber exposure system; (4) Smith-Roe SL, Wyde ME, Stout MD, Winters J, Hobbs CA, Shepard KG, Green A, Kissling GE, Tice RR, Bucher JR, and Witt KL. Evaluation of the genotoxicity of cell phone radiofrequency radiation in male and female rats and mice following subchronic exposure.

Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposures)

Draft 2-1-2018

SUMMARY

The purpose of this communication is to report partial findings from a series of radiofrequency radiation (RFR) cancer studies in rats performed under the auspices of the U.S. National Toxicology Program (NTP).[1] This report contains peer-reviewed, neoplastic and hyperplastic findings only in the brain and heart of Hsd:Sprague Dawley® SD® (HSD) rats exposed to RFR starting *in utero* and continuing throughout their lifetimes. These studies found low incidences of malignant gliomas in the brain and schwannomas in the heart of male rats exposed to RFR of the two types [Code Division Multiple Access (CDMA) and Global System for Mobile Communications (GSM)] currently used in U.S. wireless networks. Potentially preneoplastic lesions were also observed in the brain and heart of male rats exposed to RFR.

The review of partial study data in this report has been prompted by several factors. Given the widespread global usage of mobile communications among users of all ages, even a very small increase in the incidence of disease resulting from exposure to RFR could have broad

[1] NTP is a federal, interagency program, headquartered at the National Institute of Environmental Health Sciences, part of the National Institutes of Health, whose goal is to safeguard the public by identifying substances in the environment that may affect human health. For more information about NTP and its programs, visit http://ntp.niehs.nih.gov

Report Revised on February 1, 2018

implications for public health. There is a high level of public and media interest regarding the safety of cell phone RFR and the specific results of these NTP studies.

Lastly, the tumors in the brain and heart observed at low incidence in male rats exposed to GSM- and CDMA-modulated cell phone RFR in this study are of a type similar to tumors observed in some epidemiology studies of cell phone use. These findings appear to support the International Agency for Research on Cancer (IARC) conclusions regarding the possible carcinogenic potential of RFR.[2]

It is important to note that this document reviews only the findings from the brain and heart and is not a complete report of all findings from the NTP's studies. Additional data from these studies in Hsd:Sprague Dawley® SD® (Harlan) rats and similar studies conducted in B6C3F_1/N mice are currently under evaluation and will be reported together with the current findings in two forthcoming NTP Technical Reports.

STUDY RATIONALE

Cell phones and other commonly used wireless communication devices transmit information via non-ionizing radiofrequency radiation (RFR). In 2013, IARC classified RFR as a *possible human carcinogen* based on "limited evidence" of an association between exposure to RFR from heavy wireless phone use and glioma and acoustic neuroma (vestibular schwannoma) in human epidemiology studies, and "limited evidence" for the carcinogenicity of RFR in experimental animals. While ionizing radiation is a well-accepted human carcinogen, theoretical arguments

[2] IARC (International Agency for Research on Cancer). 2013. Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields. IARC Monogr Eval Carcinog Risk Hum 102. Available: http://monographs.iarc.fr/ENG/Monographs/vol102/mono102.pdf [accessed 26 May 2016].

have been raised against the possibility that non-ionizing radiation could induce tumors (discussed in IARC, 2013). Given the extremely large number of people who use wireless communication devices, even a very small increase in the incidence of disease resulting from exposure to the RFR generated by those devices could have broad implications for public health.

DESCRIPTION OF THE NTP CELL PHONE RFR PROGRAM

RFR emitted by wireless communication devices, especially cell phones, was nominated to the NTP for toxicology and carcinogenicity testing by the U.S. Food and Drug Administration (FDA). After careful and extensive evaluation of the published literature and experimental efforts already underway at that time, the NTP concluded that additional studies were warranted to more clearly define any potential health hazard to the U.S. population. Due to the technical complexity of such studies, NTP staff worked closely with RFR experts from the National Institute of Standards and Technology (NIST). With support from NTP, engineers at NIST evaluated various types of RFR exposure systems and demonstrated the feasibility of using a specially designed exposure system (reverberation chambers), which resolved the inherent limitations identified in existing systems.

In general, NTP chronic toxicity/carcinogenicity studies expose laboratory rodents to a test article for up to 2 years and are designed to determine the potential for the agent tested to be hazardous and/or carcinogenic to humans.[3] For cell phone RFR, a program of study was designed to evaluate potential, long-term health effects of whole-body exposures. These studies were conducted in three phases: (1) a series of pilot studies to establish field strengths that do not raise body temperature, (2) 28-day toxicology studies in rodents exposed to various low-level

[3] Specifications for the Conduct of NTP Studies, http://ntp.niehs.nih.gov/ntp/test_info/finalntp_toxcarspecsjan2011.pdf

field strengths, and (3) chronic toxicology and carcinogenicity studies. The studies were carried out under contract at IIT Research Institute (IITRI) in Chicago, IL following Good Laboratory Practices (GLP). These studies were conducted in rats and mice using a reverberation chamber exposure system with two signal modulations [Code Division Multiple Access (CDMA) and Global System for Mobile Communications (GSM)] at two frequencies (900 MHz for rats and 1900 MHz for mice), the modulations and frequency bands that are primarily used in the United States.

STUDY DESIGN

Hsd:Sprague Dawley® SD® (Harlan) rats were housed in custom-designed reverberation chambers and exposed to cell phone RFR. Experimentally generated 900 MHz RF fields with either GSM or CDMA modulation were continuously monitored in real-time during all exposure periods via RF sensors located in each exposure chamber that recorded RF field strength (V/m). Animal exposure levels are reported as whole-body specific absorption rate (SAR), a biological measure of exposure based on the deposition of RF energy into an absorbing organism or tissue. SAR is defined as the energy (watts) absorbed per mass of tissue (kilograms). Rats were exposed to GSM- or CDMA-modulated RFR at 900 MHz with whole-body SAR exposures of 0, 1.5, 3, or 6 W/kg. RFR field strengths were frequently adjusted based on changes in body weight to maintain desired SAR levels.

Exposures to RFR were initiated *in utero* beginning with the exposure of pregnant dams (approximately 11-14 weeks of age) on Gestation Day (GD) 5 and continuing throughout gestation. After birth, dams and pups were exposed in the same cage through weaning on postnatal day (PND) 21, at which point the dams were removed and exposure of 90 pups per sex

per group was continued for up to 106 weeks. Pups remained group-housed from PND 21 until they were individually housed on PND 35. Control and treatment groups were populated with no more than 3 pups per sex per litter. All RF exposures were conducted over a period of approximately 18 hours using a continuous cycle of 10 minutes on (exposed) and 10 minutes off (not exposed), for a total daily exposure time of approximately 9 hours a day, 7 days/week. A single, common group of unexposed animals of each sex served as controls for both RFR modulations. These control rats were housed in identical reverberation chambers with no RF signal generation. Each chamber was maintained on a 12-hour light/dark cycle, within a temperature range of 72 ± 3°F, a humidity range of 50 ± 15%, and with at least 10 air changes per hour. Throughout the studies, all animals were provided *ad libitum* access to feed and water.

RESULTS

In pregnant rats exposed to 900 MHz GSM- or CDMA-modulated RFR, no exposure-related effects were observed on the percent of dams littering, litter size, or sex distribution of pups. Small, exposure-level-dependent reductions (up to 7%) in body weights compared to controls were observed throughout gestation and lactation in dams exposed to GSM- or CDMA-modulated RFR. In the offspring, litter weights tended to be lower (up to 9%) in GSM and CDMA RFR-exposed groups compared to controls. Early in the lactation phase, body weights of male and female pups were lower in the GSM-modulated (8%) and CDMA-modulated (15%) RFR groups at 6 W/kg compared to controls. These weight differences in the offspring for both GSM and CDMA exposures tended to lessen (6% and 10%, respectively) as lactation progressed. Throughout the remainder of the chronic study, no RFR exposure-related effects on body weights were observed in male and female rats exposed to RFR, regardless of modulation

(Figures 1 and 2). At the end of the 2-year study, survival was lower in the control group of males than in all groups of male rats exposed to GSM-modulated RFR (Figure 3).

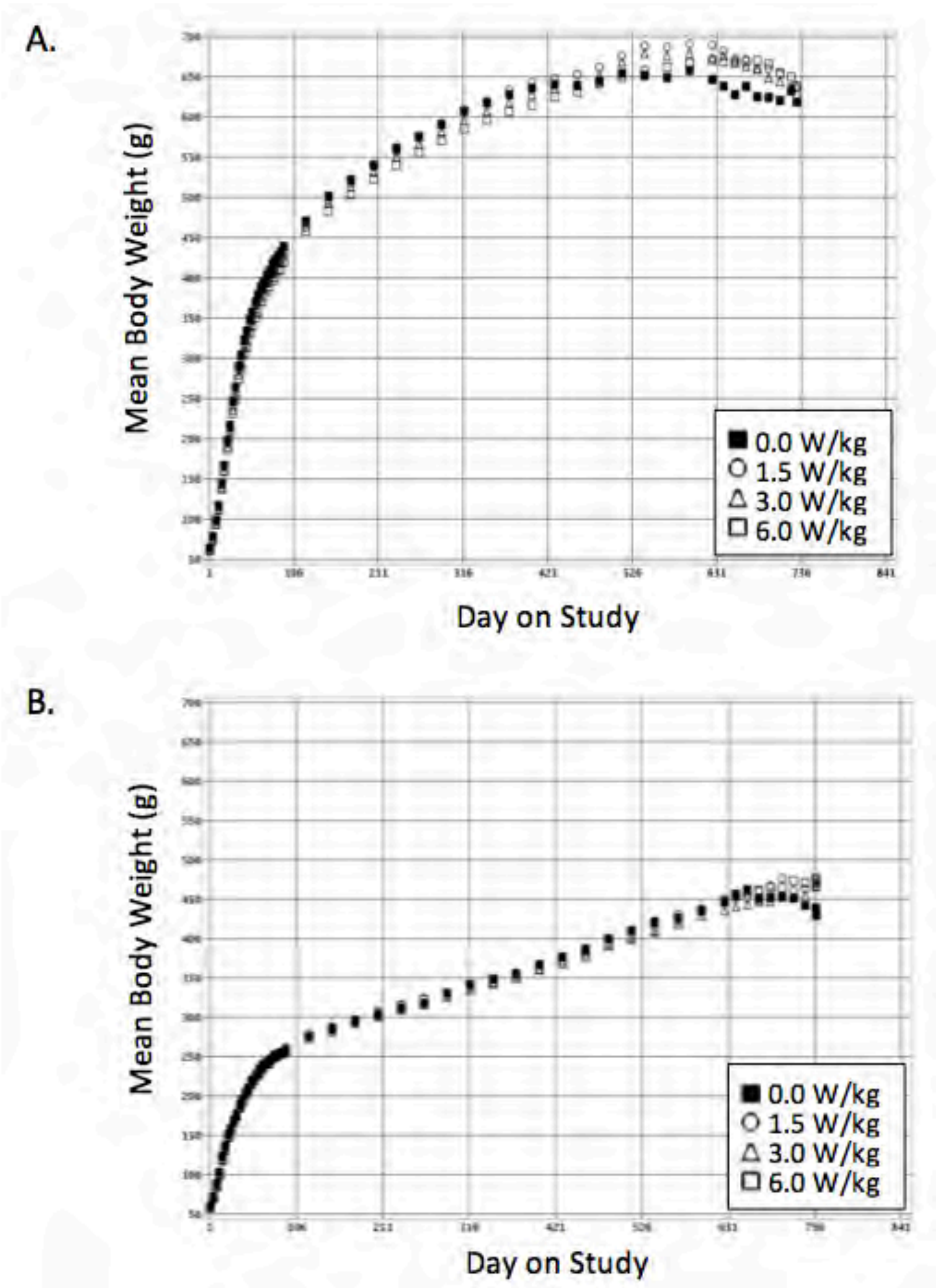

Figure 1. Growth Curves for Male (A) and Female (B) Rats Exposed to Whole Body GSM-Modulated RFR for 2 Years

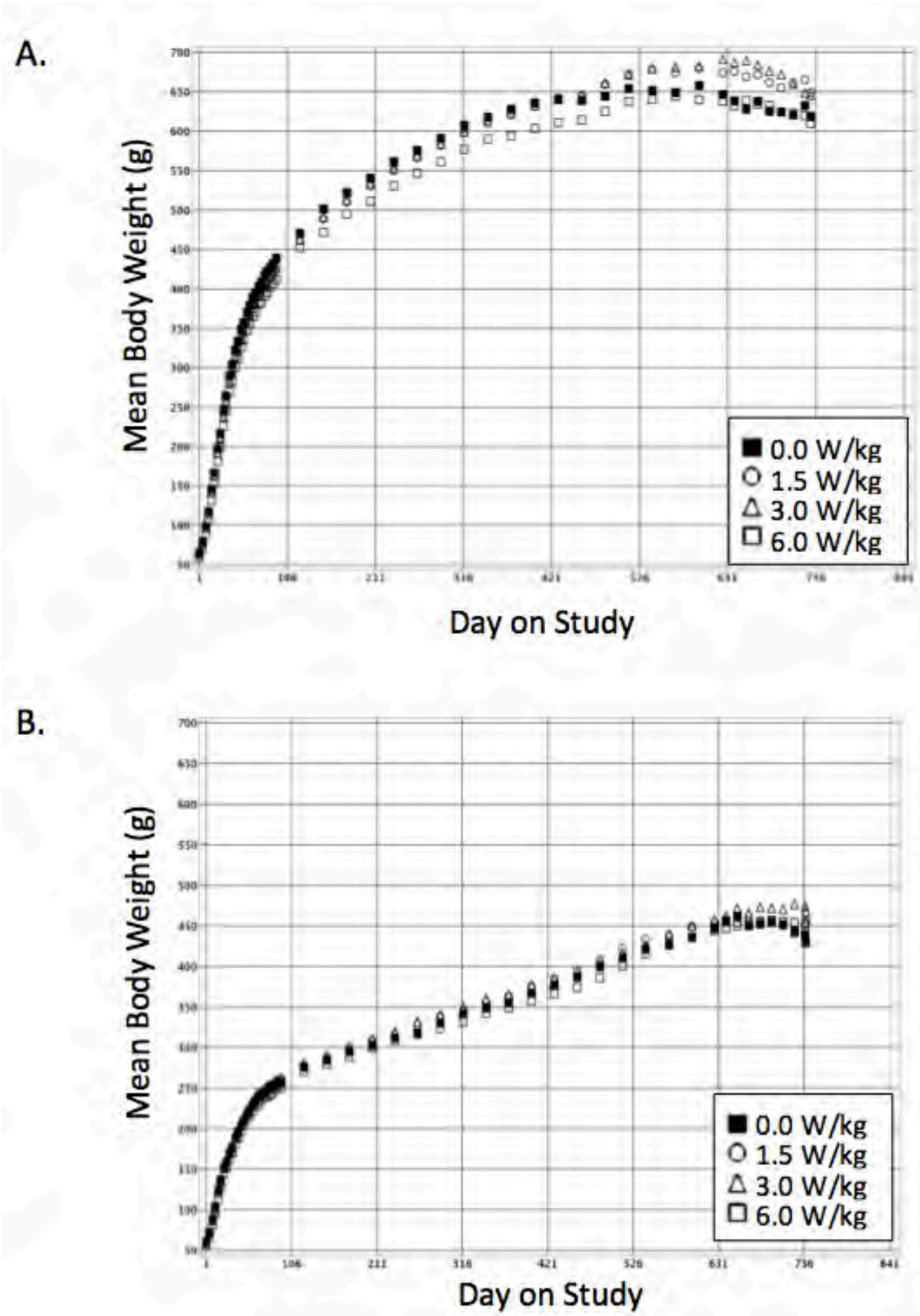

Figure 2. Growth Curves for Male (A) and Female (B) Rats Exposed to Whole Body CDMA-Modulated RFR for 2 Years

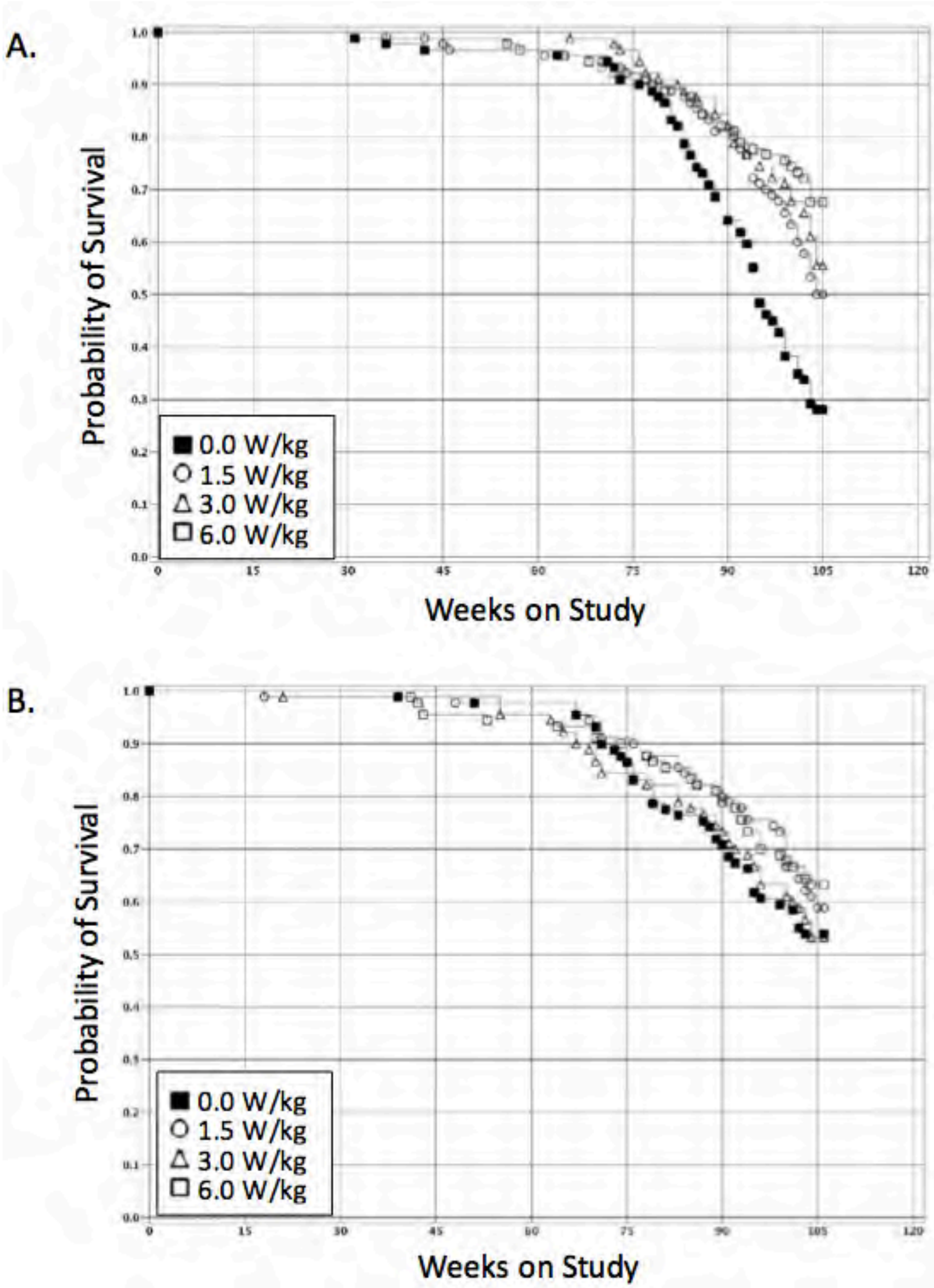

Figure 3. Kaplan-Meier Survival Curves for Male (A) and Female (B) Rats Exposed to Whole Body GSM-Modulated RFR for 2 Years

Survival was also slightly lower in control females than in females exposed to 1.5 or 6 W/kg GSM-modulated RFR. In rats exposed to CDMA-modulated RFR, survival was higher in all groups of exposed males and in the 6 W/kg females compared to controls (Figure 4).

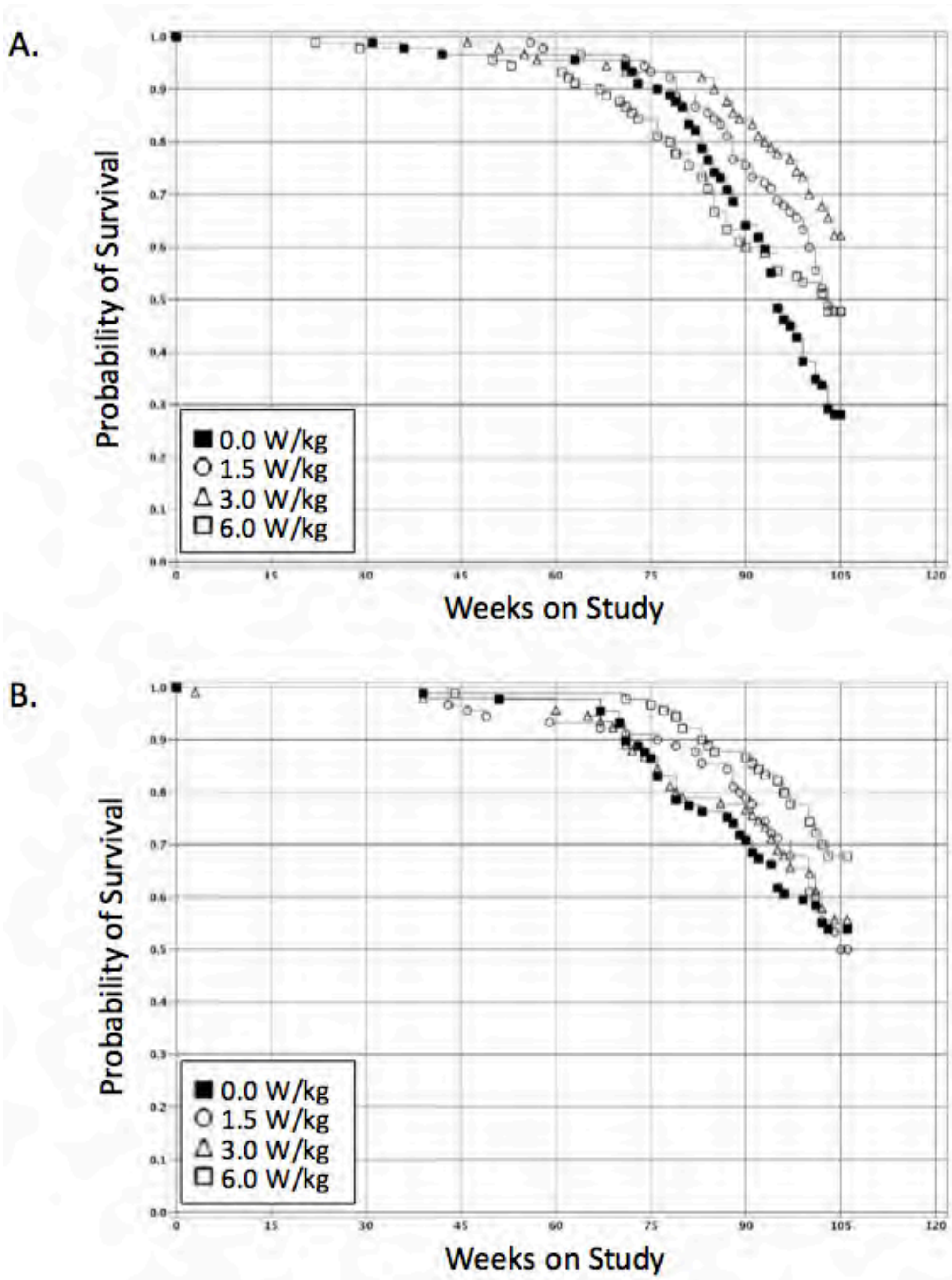

Figure 4. Kaplan-Meier Survival Curves for Male (A) and Female (B) Rats Exposed to Whole Body CDMA-Modulated RFR for 2 Years

Brain

A low incidence of malignant gliomas and glial cell hyperplasia was observed in all groups of male rats exposed to GSM-modulated RFR (Table 1). In males exposed to CDMA-modulated RFR, a low incidence of malignant gliomas occurred in rats exposed to 6 W/kg (Table 1). Glial cell hyperplasia was also observed in the 1.5 W/kg and 6 W/kg CDMA-modulated exposure groups. No malignant gliomas or glial cell hyperplasias were observed in controls. There was not a statistically significant difference between the incidences of lesions in exposed male rats compared to control males for any of the GSM- or CDMA-modulated RFR groups. However, there was a statistically significant positive trend in the incidence of malignant glioma ($p < 0.05$) for CDMA-modulated RFR exposures.

Table 1. Incidence of brain lesions in male Hsd:Sprague Dawley® SD® (Harlan) rats exposed to GSM- or CDMA-modulated RFR§

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Malignant glioma † ‡	0*	3 (3.3%)	3 (3.3%)	2 (2.2%)	0	0	3 (3.3%)
Glial cell hyperplasia	0	2 (2.2%)	3 (3.3%)	1 (1.1%)	2 (2.2%)	0	2 (2.2%)

§ Data presented as number of animals per group with lesions (percentage of animals per group with lesions).
* Significant SAR-dependent trend for CDMA exposures by poly-6 ($p < 0.05$). See appendix B
† Poly-6 survival adjusted rates for malignant gliomas were 0/53.48 in controls; GSM: 3/67.96 (4.4%), 3/72.10 (4.2%), and 2/72.65 (2.8%) in the 1.5, 3, and 6 W/kg groups, respectively; CDMA: 0/65.94, 0/73.08, and 3/57.49 (5.2%) for the 1.5, 3, and 6 W/kg groups, respectively.
‡ Historical control incidence in NTP studies: 11/550 (2.0%), range 0-8%

In females exposed to GSM-modulated RFR, a malignant glioma was observed in a single rat exposed to 6 W/kg, and glial cell hyperplasia was observed in a single rat exposed to 3 W/kg (Table 2). In females exposed to CDMA-modulated RFR, malignant gliomas were observed in two rats exposed to 1.5 W/kg. Glial cell hyperplasia was observed in one female in each of the CDMA-modulation exposure groups (1.5, 3, and 6 W/kg). There was no glial cell hyperplasia or

malignant glioma observed in any of the control females. Detailed descriptions of the malignant gliomas and glial cell hyperplasias are presented in Appendix C.

Table 2. Incidence of brain lesions in female Hsd:Sprague Dawley® SD® (Harlan) rats exposed to GSM- or CDMA-modulated RFR[§,¶]

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Malignant glioma [‡]	0	0	0	1 (1.1%)	3 (3.3%)	0	0
Glial cell hyperplasia	0	0	1 (1.1%)	0	0	1 (1.1%)	1 (1.1%)

[§] Data presented as number of animals per group with lesions (percentage of animals per group with lesions).
[¶] February 2, 2018 update reclassifies one hyperplasia to a malignant glioma in the 1.5 W/kg CDMA group, correcting a transcription error.
[‡] Historical control incidence in NTP studies: 1/540 (0.18%), range 0-2%

Heart

Cardiac schwannomas were observed in male rats in all exposed groups of both GSM- and CDMA-modulated RFR, while none were observed in controls (Table 3). For both modulations (GSM and CDMA), there was a significant positive trend in the incidence of schwannomas of the heart with respect to exposure SAR. Additionally, the incidence of schwannomas in the 6 W/kg males was significantly higher in CDMA-modulated RFR-exposed males compared to controls. The incidence of schwannomas in the 6 W/kg GSM-modulated RFR-exposed males was higher, but not statistically significant ($p = 0.052$) compared to controls. Schwann cell hyperplasia of the heart was also observed in three males exposed to 6 W/kg CDMA-modulated RFR. In the GSM-modulation exposure groups, a single incidence of Schwann cell hyperplasia was observed in a 1.5 W/kg male and 2 in the 6W/kg group.

Table 3. Incidence of heart lesions in male Hsd:Sprague Dawley® SD® (Harlan) rats exposed to GSM- or CDMA-modulated cell phone RFR§

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Schwannoma † ‡	0*	2 (2.2%)	1 (1.1%)	5 (5.5%)	2 (2.2%)	3 (3.3%)	6 (6.6%)**
Schwann cell hyperplasia	0	1 (1.1%)	0	2 (2.2%)	0	0	3 (3.3%)

§ Data presented as number of animals per group with lesions (percentage of animals per group with lesions).
* Significant SAR level-dependent trend for GSM and CDMA by poly-3 ($p < 0.05$). See appendix B
** Significantly higher than controls by poly-3 ($p < 0.05$)
† Poly-3 survival adjusted rates for schwannomas were 0/65.47 in controls; GSM: 2/74.87 (2.7%), 1/77.89 (1.3%), and 5/78.48 (6.4%) in the 1.5, 3, and 6 W/kg groups, respectively; CDMA: 2/74.05 (2.7%), 3/78.67 (3.8%), and 6/67.94 (8.8%) for the 1.5, 3, and 6 W/kg groups, respectively.
‡ Historical control incidence in NTP studies: 9/699 (1.3%) range 0-6%

In females, schwannomas of the heart were also observed at 3 W/kg GSM-modulated RFR and 1.5 and 6 W/kg CDMA-modulated RFR. Schwann cell hyperplasia was observed in one female at 6 W/kg GSM, and in each of the CDMA-modulation exposure groups (1.5, 3, and 6 W/kg).

Table 4. Incidence of heart lesions in female Hsd:Sprague Dawley® SD® (Harlan) rats exposed to GSM- or CDMA-modulated cell phone RFR§

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Schwannoma‡	0	0	2 (2.2%)	0	2 (2.2%)	0	2 (2.2%)
Schwann cell hyperplasia	0	0	0	1 (1.1%)	1 (1.1%)	1 (1.1%)	1 (1.1%)

§ Data presented as number of animals per group with tumors (percentage of animals per group with tumors).
‡ Historical control incidence in NTP studies: 4/699 (0.6 %), range 0-4%

Schwann cells are present in the peripheral nervous system and are distributed throughout the whole body, not just in the heart. Therefore, organs other than the heart were examined for schwannomas and Schwann cell hyperplasia. Several occurrences of schwannomas were observed in the head, neck, and other sites throughout the body of control and GSM and CDMA

RFR-exposed male rats. In contrast to the significant increase in the incidence of schwannomas in the heart of exposed males, the incidence of schwannomas observed in other tissue sites of exposed males (GSM and CDMA modulations) was not significantly different than in controls (Table 5). Additionally, Schwann cell hyperplasia was not observed in any tissues other than the heart. The combined incidence of schwannomas from all sites was generally higher in GSM- and CDMA-modulated RFR exposed males, but not significantly different than in controls. The Schwann cell response to RFR appears to be specific to the heart of male rats.

Table 5. Incidence of schwannomas in male Hsd:Sprague Dawley® SD® (Harlan) rats exposed to GSM- or CDMA-modulated RFR§,¶

	Control	GSM			CDMA		
	0 W/kg	1.5 W/kg	3 W/kg	6 W/kg	1.5 W/kg	3 W/kg	6 W/kg
Number examined	90	90	90	90	90	90	90
Heart‡	0*	2 (2.2%)	1 (1.1%)	5 (5.5%)	2 (2.2%)	3 (3.3%)	6 (6.6%)**
Other sites†	3 (3.3%)	1 (1.1%)	4 (4.4%)	2 (2.2%)	2 (2.2%)	1 (1.1%)	2 (2.2%)
All sites (total)	3 (3.3%)	3 (3.3%)	5 (5.5%)	7 (7.7%)	4 (4.4%)	4 (4.4%)	8 (8.8%)

§ Data presented as number of animals per group with tumors (percentage of animals per group with tumors).
¶ February 2, 2018 update adds one additional tumor in the 6 W/kg CDMA group, identified as a result of additional pathology reviews of other sites.
* Significant SAR level-dependent trend for GSM and CDMA, poly 3 test ($p < 0.05$)
** Significantly higher than controls, poly-3 test ($p < 0.05$)
‡ Historical control incidence in NTP studies: 9/699 (1.3%), range 0-6%
† Mediastinum, thymus, and fat

In female rats, there was no statistically significant or apparent exposure-related effect on the incidence of schwannomas in the heart or the combined incidence in the heart or other sites (Table 6).

Table 6. Incidence of schwannomas in female Hsd:Sprague Dawley® SD® (Harlan) rats exposed to GSM- or CDMA-modulated RFR[§]

Schwannoma site	Control 0 W/kg	GSM 1.5 W/kg	GSM 3 W/kg	GSM 6 W/kg	CDMA 1.5 W/kg	CDMA 3 W/kg	CDMA 6 W/kg
Number examined	90	90	90	90	90	90	90
Heart[‡]	0	0	2 (2.2%)	0	2 (2.2%)	0	2 (2.2%)
Other sites[†]	4 (4.4%)	1 (1.1%)	3 (3.3%)	2 (2.2%)	0	2 (2.2%)	2 (2.2%)
All sites (total)	4 (4.4%)	1 (1.1%)	5 (5.5%)	2 (2.2%)	2 (2.2%)	2 (2.2%)	4 (4.4%)

[§] Data presented as number of animals per group with tumors (percentage of animals per group with tumors).
[‡] Historical control incidence in NTP studies: 4/699 (0.6%), range 0-4%
[†] Ovary, uterus, vagina, thymus, abdomen, and clitoral gland

DISCUSSION

The two tumor types, which are the focus of this report, are malignant gliomas of the brain and schwannomas of the heart. Glial cells are a collection of specialized, non-neuronal, support cells whose functions include maintenance of homeostasis, formation of myelin, and providing support and protection for neurons of the peripheral nervous system (PNS) and the central nervous system (CNS). In the CNS, glial cells include astrocytes, oligodendrogliocytes, microglial cells, and ependymal cells. Schwann cells are classified as glial cells of the PNS. In the PNS, Schwann cells produce myelin and are analogous to oligodendrocytes of the CNS. Generally, glial neoplasms in the rat are aggressive, poorly differentiated, and usually classified as malignant.

In the heart, exposure to GSM or CDMA modulations of RFR in male rats resulted in a statistically significant, positive trend in the incidence of schwannomas. There was also a statistically significant, pairwise increase at the highest CDMA exposure level tested compared to controls. Schwann cell hyperplasias also occurred at the highest exposure level of CDMA-

modulated RFR. The intracardiac schwannomas in male rats were not observed in animals from the same litter. Schwann cell hyperplasia in the heart may progress to cardiac schwannomas. No Schwann cell hyperplasias or schwannomas of the heart were observed in the single, common control group of male rats. The historical control rate of schwannomas of the heart in male Harlan Sprague Dawley rats is 1.30% (7/539) and ranges from 0-6% for individual NTP studies (Table D2, Appendix D). The 5.5-6.6% observed in the 6 W/kg GSM- and CDMA-modulated RFR groups exceeds the historical incidence, and approaches or exceeds the highest rate observed in a single study (6%). The increase in the incidence of schwannomas in the heart of male rats in this study is likely the result of whole-body exposures to GSM- or CDMA-modulated RFR.

In the brain, there was a significant, positive trend in the incidences of malignant gliomas in males exposed to CDMA-modulated RFR, and a low incidence was observed in males at all exposure levels of GSM-modulated RFR that was not statistically different than in control males. The male rats in which gliomas were observed were not from the same litter. Glial cell hyperplasia, a preneoplastic lesion distinctly different from gliosis, was also observed at low incidences in rats exposed to either GSM or CDMA modulation. Glial cell hyperplasia may progress to malignant glioma. Neither of these lesions was observed in the control group of male rats. Although not observed in the current control group, malignant gliomas have been observed in control male Harlan Sprague Dawley rats from other completed NTP studies. Currently in males, the historical control rate of malignant glioma for those studies is 2.0% (11/550) and ranges from 0-8% for individual studies (Table D1, Appendix D). The 2.2-3.3% observed in all

of the GSM-modulation groups and in the 6 W/kg CDMA-modulated group only slightly exceeds the mean historical control rate and falls within the observed range.

The survival of the control group of male rats in the current study (28%) was relatively low compared to other recent NTP studies in Hsd:Sprague Dawley® SD® (Harlan) rats (average 47%, range 24-72%). If malignant gliomas or schwannomas are late-developing tumors, the absence of these lesions in control males in the current study could conceivably be related to the shorter longevity of control rats in this study. Appendix E lists the time on study for each animal with a malignant glioma or heart schwannoma. Most of the gliomas were observed in animals that died late in the study, or at the terminal sacrifice. However, a relatively high number of the heart schwannomas in exposed groups were observed by 90 weeks into the study, a time when approximately 60 of the 90 control male rats remained alive and at risk for developing a tumor.

CONCLUSIONS

Under the conditions of these 2-year studies, the hyperplastic lesions and glial cell neoplasms of the heart and brain observed in male rats are considered likely the result of whole-body exposures to GSM- or CDMA-modulated RFR. There is higher confidence in the association between RFR exposure and the neoplastic lesions in the heart than in the brain. No biologically significant effects were observed in the brain or heart of female rats regardless of modulation.

NEXT STEPS

The results reported here are limited to select findings of concern in the brain and heart and do not represent a complete reporting of all findings from these studies of cell phone RFR. The

complete results for all NTP studies on the toxicity and carcinogenicity of GSM and CDMA-modulated RFR are currently being reviewed and evaluated according to the established NTP process and will be reported together with the current findings in two forthcoming NTP Technical Reports. Given the large scale and scope of these studies, completion of this process is anticipated by fall 2017, and the draft NTP Technical Reports are expected to be available for peer review and public comment in early 2018. We anticipate that the results from a series of initial studies investigating the tolerance to various power levels of RFR, including measurements of body temperatures in both sexes of young and old rats and mice and in pregnant female rats, will be published in the peer-reviewed literature in early 2018 as well.

APPENDIX A – CONTRIBUTORS

NTP CONTRIBUTORS

Participated in the evaluation and interpretation of results and the reporting of findings.

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APPENDIX B – STATISTICAL ANALYSIS

Appendix B1: Statistical Methods

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of lesion incidence at a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power. This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter, k, for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). A further advantage of the Poly-k method is that it does not require lesion lethality assumptions.

Unless otherwise specified, the NTP uses a value of k=3 in the analysis of site-specific lesions (Portier et al., 1986). Bailer and Portier (1988) showed that the Poly-3 test gives valid results if the true value of k is anywhere in the range from 1 to 5. In addition, Portier et al. (1986) modeled a collection of relatively common tumors observed in control animals from two-year NTP rodent carcinogenicity studies, showing that the Weibull distribution with values of k ranging between 1 and 5 was a reasonable fit to tumor incidence in most cases. In cases of early tumor onset or late tumor onset, however, k=3 may not be the optimal choice. Tumors with early onset would require a value of k much less than 3, while tumors with late onset would require a value of k much greater than 3. In the current studies, malignant brain gliomas occurred only in animals surviving more than 88% of the length of the study. For these brain tumors, a Weibull distribution with k=6 is a better fit to survival time than with k=3 (Portier, 1986). Malignant schwannomas of the heart occurred in animals surviving at least 65% of the length of the study; a Weibull distribution with k=3 adequately fits these heart tumor incidences. Therefore, poly-6 tests were used for analyses of brain tumors and poly-3 tests were used for schwannomas.

Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-k statistic as recommended by Bieler and Williams (1993) and a continuity correction modified from Thomas et al. (1977) was applied.

Tests of significance for tumors and nonneoplastic lesions included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. Continuity-corrected Poly-k tests were used in the analysis of lesion incidence, and reported P values are one sided.

Body weights and litter weights were compared to the control group using analysis of variance and Dunnett's test (1955). The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958). Statistical analyses for possible exposure-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify exposure-related trends. Survival analysis p-values are two-sided.

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Appendix B2: Statistical Significance of Rare Tumors in a Low Powered Situation - NTP View

In Dr. Lauer's review (Appendix G1, p 47) he states: "The low power implies that there is a high risk of false positive findings, especially since the epidemiological literature questions the purported association between cell phone exposure and cancer." He kindly provided three additional references (cited below) to justify his statement.

The three papers make the argument that in studies that have low power to detect an effect, a significant finding (*p* value <0.05) is more likely to be a false positive than a true positive. In some cases this may be correct, but for rare tumors, as observed in the current study, it is very unlikely that the significant findings are false positives. One reason for this is that the actual significance level of the tests is not 0.05; it is <u>much</u> less, as illustrated below. Another reason is the introduction and use of rates of true prevalence of effects, which we consider first.

A few definitions are useful:

The significance level of the test, α, is the probability of a false positive. The power of the test, $1 - \beta$, is the probability of a true positive. Following the notation in the Button *et al.* (2013) reference, the Positive Predictive Value, *PPV*, is the probability that a statistically significant result is a true positive.

$$PPV = \frac{[1-\beta]\times R}{[1-\beta]\times R + \alpha}$$

This expression involves *R*, which is the pre-study odds that the tested effect is a true effect. That is,

$$R = \frac{\Pr(Tested\ Effect\ is\ a\ True\ Positive)}{\Pr(Tested\ Effect\ is\ a\ True\ Negative)}$$

As illustrated below in the statistical examples, *R* is a major modifying factor governing whether a result with a significant *p* value is appropriately considered a true or false positive. The selection of an appropriate *R*, or expected odds of an effect, in this case a carcinogenic effect*,

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permits the introduction of bias in the interpretation of the *p* values in this report on the NTP cancer studies of radiofrequency radiation.

For example, *R* could be pre-assigned as the expected odds of a positive cancer finding at any site in male or female rats or mice (as in scenario 1 below where R = 1.2), or as the odds of a positive cancer finding in only the male rat (as in scenario 2 below where R = 0.54). In these two cases, the chances of our findings being true positives (*PPV*) are very high (>94%), despite the low power of the current study to detect such an effect.

R could alternatively be pre-assigned as the odds of seeing these specific tumor types occur only in the brain and/or heart of male rats. In this case, because gliomas and schwannomas have only been part of two positive calls for cancer in male rats in any of the prior studies of chemical agents that NTP has performed, *R* is much lower (0.035) and the chance of a false positive finding is indeed high. But, this is the case even if the power to detect an effect is high; i.e., the conclusion of false positivity is driven more by the *a priori* expectation of a low odds of occurrence of an effect than it is by the power to detect the effect. At high values of *R* ($R>1$), all outcomes that are $p<0.05$, regardless of the actual power, will generally be considered "true positives." At very low values of *R* ($R<0.01$), even an outcome from a study that has high power, will be considered a false positive ($PPV<0.2$).

Dr. Lauer's comment, "the epidemiological literature questions the purported association between cell phone exposure and cancer," would place the expected *R* close to zero. As can be seen at very low values of *R* approaching zero, all findings, regardless of the power to detect them, will be considered false positives. On the other hand, if one is open to the possibility that *R* is in fact non-zero, then the findings need to become part of the public discussion over the safety of exposures to RFR.

STATISTICAL EXAMPLES

To illustrate, suppose that the background tumor rate is 1.5%, which is similar to the rate of schwannomas in the hearts of male rats in the NTP historical control database (1.3%), and that there are two groups: Control and Treated, with n = 90 animals per group. Further suppose that the null hypothesis that tumor rates are the same in the two groups, H_0, is tested against the alternative hypothesis that the Treated group has a higher rate, H_a, using a one-sided Fisher's

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exact test. We reject the null hypothesis if p is less than 0.05. The actual significance level of this test, α, is the probability of rejecting the null hypothesis when is it actually true. In other words,

$$\alpha = \Pr(p < 0.05 \mid H_0\!: Tumor\ rate = 0.015\ in\ both\ groups)$$

By Fisher's exact test, $p < 0.05$ if there are

- 0 tumors in the Control group and 5 or more in the Treated group, or
- 1 tumor in the Control group and 7 or more in the Treated group, or
- 2 tumors in the Control group and 8 or more in the Treated group, or
- 3 tumors in the Control group and 10 or more in the Treated group, or
- ….

The probability of making a Type I error (false positive decision, rejecting H_0 when it is true) is:

$$\alpha = \Pr(p < 0.05 \mid H_0\!: Tumor\ rate = 0.015\ in\ both\ groups)$$

$$= \Pr(C = 0\ and\ T \geq 5)\ + \Pr(C = 1\ and\ T\ \geq 7)$$

$$+ P(C = 2\ and\ T\ \geq 8)\ + P(C = 3\ and\ T\ \geq 10) + \cdots$$

Using binomial probabilities,

$$\alpha = \left\{\binom{90}{0} 0.015^0 (1 - 0.015)^{90-0} \sum_{k=5}^{90} \binom{90}{k} 0.015^k (1 - 0.015)^{90-k}\right\}$$

$$+ \left\{\binom{90}{1} 0.015^1 (1 - 0.015)^{90-1} \sum_{k=7}^{90} \binom{90}{k} 0.015^k (1 - 0.015)^{90-k}\right\}$$

$$+ \left\{\binom{90}{2} 0.015^2 (1 - 0.015)^{90-2} \sum_{k=8}^{90} \binom{90}{k} 0.015^k (1 - 0.015)^{90-k}\right\}$$

$$+ \left\{\binom{90}{3} 0.015^3 (1 - 0.015)^{90-3} \sum_{k=10}^{90} \binom{90}{k} 0.015^k (1 - 0.015)^{90-k}\right\}$$

$$+ \ldots$$

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$$= \{0.256602 \times 0.011659\} + \{0.351689 \times 0.000431\}$$

$$+\{0.238327 \times 0.000067\} + \{0.106461 \times 0.000001\} + \cdots$$

$$= 0.00316$$

Thus, when the tumor rate is low and the decision rule is to reject H_0 when the one-sided Fisher's exact p-value is less than 0.05, the actual false positive rate, α, is 0.0032.

This significance level can be used to calculate the probability that a significant result is a true positive, Positive Predictive Value (*PPV*). Following the Button *et al.* (2013) paper's notation:

$$PPV = \frac{[1-\beta] \times R}{[1-\beta] \times R + \alpha}$$

Suppose that the power, $1 - \beta$, is 10%. *R* as defined in Button *et al.* is the pre-study odds of a true positive. There are several possible ways to estimate *R*:

1) Among the 595 NTP studies that have a determination about carcinogenesis, 326 concluded that the test article was carcinogenic*. The pre-study odds of a carcinogenic effect, *R*, is 326/(595-326) = 1.2119. Thus, the probability that a significant test represents a true positive is

$$PPV = \frac{0.10 \times 1.2119}{0.10 \times 1.2119 + 0.0032} = 0.97$$

This says that, under the low power/low tumor rate conditions described above, if a test is significant at the 0.05 level, it almost certainly indicates a real carcinogenic effect.

2) Alternatively, among the 580 NTP studies that involved male rats, 203 concluded that the test article was carcinogenic in male rats; thus, *R* = 203/(580 – 203) = 0.538 and *PPV* = 0.94.

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3) If there is no prior information and it is thought that it is as equally likely that there is a real effect as it is that there is no effect, then $R = 1$ and $PPV = 0.97$.

Furthermore, the relationship between R and PPV can be rearranged to solve for R,

$$R = \frac{\alpha}{1-\beta} \times \frac{PPV}{1-PPV} = \frac{0.00316}{0.1} \times \frac{PPV}{1-PPV}$$

In this low power/low tumor rate situation, R could be as low as 0.28 and the PPV would be at least 90%, or R could be as low as 0.13 and the PPV would be at least 80%.

Dr. Grace Kissling, NTP study statistician, provided the statistical illustrations. Also Dr. Shyamal Peddada, Acting Chief, Biostatistics and Computational Biology Branch, NIEHS, has reviewed and concurs with her interpretation of the issues posited by the papers and the explanation of why they do not diminish the importance of the findings from the current study.

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*The term “carcinogenic” in this case refers to NTP studies in which any group of male or female rats or mice was judged to show “clear” or “some” evidence of carcinogenic activity. Keep in mind that many of these agents were selected for cancer studies based on a suspicion that they would cause cancer. Other agents, such as cell phone RFR, were chosen based more on the sheer numbers of people exposed. The “level of evidence” definitions are indicated below. As one can see, statistical significance is only one of many considerations that go into the study interpretation.

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We have not assigned a specific level of evidence to the NTP RFR study, as it is not complete. Rather, we evaluated the partial study findings and concluded that the tumors highlighted are "likely" related to the RFR exposure.

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EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of evidence observed in each experiment: two categories for positive results **(clear evidence and some evidence)**; one category for uncertain findings **(equivocal evidence)**; one category for no observable effects **(no evidence)**; and one category for experiments that cannot be evaluated because of major flaws **(inadequate study)**. These categories of interpretative conclusions were first adopted in June 1983 and then revised on March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following

Added to Appendix B on June 23, 2016

convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as "were also related" to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as "may have been" related to chemical exposure.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

Added to Appendix B on June 23, 2016

APPENDIX C – PATHOLOGY

Pathology data presented in this report on cell phone RFR were subjected to a rigorous peer review process. The primary goal of the NTP peer-review process is to reach consensus agreement on treatment-related findings, confirm the diagnosis of all neoplasms, and confirm any unusual lesions. At study termination, a complete necropsy and histopathology evaluation was conducted on every animal. The initial pathology examination was performed by a veterinary pathologist, who recorded all neoplastic and nonneoplastic lesions. This examination identified several potential treatment-related lesions in target organs of concern (brain and heart), which were chosen for immediate review.[1] The initial findings of glial cell tumors and hyperplasias in the brain and schwannomas, Schwann call hyperplasia, and schwannomas from all sites were subjected to an expedited, multilevel NTP pathology peer-review process. The data were locked[2] prior to receipt of the finalized, study-laboratory reports to ensure that the raw data did not change during the review.

The pathology peer review consisted of a quality assessment (QA) review of all slides with tissues from the central nervous system (7 sections of brain and 3 sections of spinal cord), trigeminal nerve and ganglion, and heart. Additionally, the schwannomas of the head and neck region were reviewed. The QA review of the central nervous system and head and neck schwannomas was performed by Dr. Margarita Gruebbel of Experimental Pathology Laboratories, Inc. (EPL), and the QA review of the hearts and trigeminal nerves and ganglia was performed by Dr. Cynthia Shackelford, EPL.

The QA review pathologists then met with Dr. Mark Cesta, NTP pathologist for these studies, and Dr. David Malarkey, head of the NTP Pathology Group, to review lesions and select slides for the Pathology Working Group (PWG) reviews. All PWG reviews were conducted blinded with respect to treatment group and only identified the test articles as “test agent A” or “test

[1] Pathology peer review of remaining lesions from the cell phone RFR studies continues and is not addressed in this report.
[2] Locking data refers to restricting access to the computer database so the data for a particular study cannot be changed.

agent B". Due to the large number of slides for review, the PWG was held in three separate sessions:

- January 29, 2016, for review of glial lesions in the brain and Schwann cell lesions in the heart
- February 11, 2016, for review of schwannomas of the head and neck
- February 12, 2016, for review of granular cell lesions of the brain

The reviewing PWG pathologists largely agreed on the diagnostic criteria for the lesions and on the diagnoses of schwannomas in the head and neck, and granular cell lesions in the brain. However, there was much discussion on the criteria for differentiating glial cell hyperplasia from malignant glioma and Schwann cell hyperplasia from schwannoma. The lack of PWG agreement on definitive criteria for the glial cell and Schwann cell lesions, and the requirement for a high level of confidence in the diagnoses prompted NTP to convene two additional PWGs (organized and conducted by the NTP pathologist, Dr. Mark Cesta) with selected experts in the organ under review. These second level PWG reviews were also conducted as noted above and held in two separate sessions:

- February 25, 2016, for review of glial lesions in the brain
- March 3, 2016, for review of cardiac schwannomas, schwannomas in other organs (except the head and neck), and right ventricular degeneration

In both PWGs, the participants came to consensus on the diagnoses of the lesions and the criteria used for those diagnoses. Participants of the individual PWGs are listed below.

Table C-1. NTP Pathology Working Group (PWG) Attendees

PWG member	Affiliation
January 29, 2016 - Evaluated glial lesions in the brain and Schwann cell lesions in the heart	
A.E. Brix, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences
G.P. Flake, M.D.	National Institute of Environmental Health Sciences
R.H. Garman, D.V.M.	Consultants in Veterinary Pathology, Inc. Monroeville, PA
M.M. Gruebbel, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC (observer)
R.A. Herbert, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
J.S. Hoane, D.V.M.	Charles River Laboratories, Inc. Durham, NC (contract study pathologist)
K.S. Janardhan, BVSc, MVSc, Ph.D.	Integrated Laboratory System
R. Kovi, BVSc, MVSc, Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC (observer)
D.E. Malarkey, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
R.A. Miller, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
J.P. Morrison, D.V.M.	Charles River Laboratories, Inc. Durham, NC

PWG member	Affiliation
A.R. Pandiri, BVSc & AH, Ph.D.	National Institute of Environmental Health Sciences
C.C. Shackelford, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC (observer)
J.A. Swenberg, D.V.M., Ph.D.	University of North Carolina – Chapel Hill, NC
G. Willson, BVMS, Dip RC Path, FRC Path, MRCVS	Experimental Pathology Laboratories, Inc. RTP, NC (PWG coordinator)
February 11, 2016 - Evaluated schwannomas of the head and neck	
A.E. Brix, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences
G.P. Flake, M.D.	National Institute of Environmental Health Sciences
M.M. Gruebbel, D.V.M., Ph.D.,	Experimental Pathology Laboratories, Inc. RTP, NC (PWG coordinator)
K.S. Janardhan, BVSc, MVSc, Ph.D.	Integrated Laboratory System RTP, NC
D.E. Malarkey, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
A.R. Pandiri, BVSc & AH, Ph.D.	National Institute of Environmental Health Sciences
R.R. Maronpot, D.V.M.	Experimental Pathology Laboratories, Inc. RTP, NC
February 12, 2016 - Evaluated granular cell lesions of the brain	
A.E. Brix, D.V.M., Ph.D.	Experimental Pathology Laboratories, Inc. RTP, NC
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences
M.M. Gruebbel, D.V.M., Ph.D.,	Experimental Pathology Laboratories, Inc. RTP, NC (PWG coordinator)
J.S. Hoane, D.V.M.	Charles River Laboratories, Inc. Durham, NC (contract study pathologist)
K.S. Janardhan, BVSc, MVSc, Ph.D.	Integrated Laboratory System RTP, NC
A.R. Pandiri, BVSc. & AH, Ph.D.	National Institute of Environmental Health Sciences
R.R. Moore, D.V.M.	Integrated Laboratory System RTP, NC
February 25, 2016 - Evaluated glial lesions in the brain	
D. Bigner, M.D., Ph.D.	Duke University Durham, NC
B. Bolon, D.V.M., MS, Ph.D.	GEMpath, Inc. Longmont, CO
V. Chen, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (observer)
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (PWG coordinator, NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences (observer)
G.P. Flake, M.D.	National Institute of Environmental Health Sciences (observer)
J.S. Hardisty, D.V.M.	Experimental Pathology Laboratories, Inc. RTP, NC
R.A. Herbert, D.V.M., Ph.D.,	National Institute of Environmental Health Sciences (observer)
R. Kovi, BVSc, MVSc, Ph.D.	Experimental Pathology Laboratories, Inc. (observer)
P.B. Little, D.V.M.	Experimental Pathology Laboratories, Inc.
D.E. Malarkey, D.V.M., Ph.D.	National Institute of Environmental Health Sciences
J.P. Morrison, D.V.M., Ph.D.	Charles River Laboratories, Inc.
A. Sharma, BVSc, MVSc, MS, Ph.D.	Covance
March 3, 2016 - Evaluated heart lesions, and schwannomas in other organs (except head and neck)	
B. Berridge, D.V.M., Ph.D.	GlaxoSmithKline RTP, NC
M.C. Boyle, D.V.M., Ph.D.	Amgen Thousand Oaks, CA
V. Chen, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (observer)
M.F. Cesta, D.V.M., Ph.D.	National Institute of Environmental Health Sciences (PWG coordinator, NTP study pathologist)
S.A. Elmore, D.V.M., MS	National Institute of Environmental Health Sciences (observer)
M. Elwell, D.V.M., Ph.D.	Covance Chantilly, VA

PWG member	Affiliation
J.R. Hailey, D.V.M.	Covance Chantilly, VA
M. Novilla, D.V.M., MS, Ph.D.	SNBL Everett, WA

LESION DESCRIPTIONS

Brain

Malignant gliomas were infiltrative lesions, usually of modest size, with indistinct tumor margins. The neoplastic cells were typically very densely packed with more cells than neuropil. The cells were typically small and had round to oval, hyperchromatic nuclei. Mitoses were infrequent. In some of the neoplasms, invasion of the meninges, areas of necrosis surrounded by palisading neoplastic cells, cuffing of blood vessels, and neuronal satellitosis were observed. The malignant gliomas did not appear to arise from any specific anatomic subsite of the brain.

Glial cell hyperplasia consisted of small, proliferative, and poorly demarcated foci of poorly differentiated glial cells that accumulated and invaded into the surrounding parenchyma. In some cases, there was a small amount of perivascular cuffing. The hyperplastic cells appeared morphologically identical to those in the gliomas but were typically less dense with more neuropil than glial cells. There were no necrotic or degenerative elements present, so there was no evidence that the increased number of glial cells was a reaction to brain injury.

Heart

The intracardiac schwannomas were either endocardial or myocardial (intramural). The endocardial schwannomas lined the ventricles and atria and invaded into the myocardium. Two morphologic cell types were observed, but indistinct cell margins and eosinophilic cytoplasm were common to both types. Groups of cells with widely spaced small, round nuclei and moderate amounts of cytoplasm were interspersed among bands or sheets of parallel, elongated cells with thin, spindle-shaped, hyperchromatic nuclei. The myocardial schwannomas were typically less densely cellular and infiltrated amid, sometimes replacing, the cardiomyocytes. The cell types described for the endocardial neoplasms were both present, but in fewer numbers. In both subtypes of schwannomas, there was a minimal amount of cellular pleomorphism. In some larger neoplasms, Antoni type A and B patterns were present.

The Schwann cell hyperplasias were similar in appearance to the schwannomas, but were smaller and had less pleomorphism of the cells. In the case of the endocardial Schwann cell hyperplasia, there was no invasion of the myocardium.

APPENDIX D – HISTORICAL CONTROLS

Table D1. Incidence of astrocytoma, glioma, and/or oligodendroglioma in brains of male Harlan Sprague Dawley rats in NTP studies

Chemical	First dose	N	Control incidence
Dibutylphthalate	8/30/2010	49	4%
2-Hydroxy-4-methoxybenzophenone	11/8/2010	50	0%
p-Chloro-a,a,a-trifluorotoluene	1/17/2011	50	4%
Di-(2-ethylhexyl)phthalate	2/17/2011	50	8%
Di-(2-ethylhexyl)phthalate (perinatal)	6/27/2011	50	0%
Tris (chloroisopropyl) phosphate	12/12/2011	50	0%
Sodium tungstate	12/23/2011	50	4%
Resveratrol	5/7/2012	50	0%
Black cohosh	7/2/2012	50	2%
Radiofrequency radiation (GSM/CDMA)	9/16/2012	90	0%

Historical control rate: 11/550 (2.0%)

Table D2. Incidence of schwannoma in the heart of male Harlan Sprague Dawley rats in NTP studies

Chemical	First dose	N	Control incidence
Indole-3-carbinol	3/14/2007	50	2%
Perfluorooctanoic acid	6/19/2009	50	0%
Dietary zinc	9/3/2009	50	0%
Dibutylphthalate	8/30/2010	49	4%
2-Hydroxy-4-methoxybenzophenone	11/8/2010	50	2%
p-Chloro-a,a,a-trifluorotoluene	1/17/2011	50	0%
Di-(2-ethylhexyl)phthalate	2/17/2011	50	6%
Di-(2-ethylhexyl)phthalate (perinatal)	6/27/2011	50	4%
Tris (chloroisopropyl) phosphate	12/12/2011	50	0%
Sodium tungstate	12/23/2011	50	0%
Resveratrol	5/7/2012	50	0%
Black Cohosh	7/2/2012	50	0%
Radiofrequency radiation (GSM/CDMA)	9/16/2012	90	0%

Historical control rate: 9/699 (1.30%)

APPENDIX E – TIME ON STUDY TO APPEARANCE OF TUMORS

Malignant Glioma

SAR (W/kg)	Animal ID number	Time on study (weeks)
GSM-modulated exposed males		
1.5	717	105
	735	102
	786	104
3.0	924	101
	943	105
	1014	93
6.0	1135	104
	1137	102
CDMA-modulated exposed males		
6.0	1795	105
	1799	104
	1852	105
GSM-modulated exposed females		
6.0	1246	96
CDMA-modulated exposed females		
1.5	1463	105
	1474	105
	1523	550

Time to Malignant Schwannoma in Heart

SAR (W/kg)	Animal ID number	Length of survival (weeks)
	GSM-modulated exposed males	
1.5	758	104
	801	105
3.0	931	105
6.0	1149	83
	1155	105
	1187	104
	1206	104
	1230	91
	CDMA-modulated exposed males	
1.5	1364	105
	1352	105
3.0	1559	92
	1617	105
	1622	104
6.0	1801	76
	1821	70
	1829	104
	1833	89
	1849	104
	1860	105
	GSM-modulated exposed females	
3.0	1037	105
	1077	83
	CDMA-modulated exposed females	
1.5	1461	106
	1480	93
6.0	1888	105
	1965	106

APPENDIX F – REVIEWERS' COMMENTS

National Toxicology Program

Peer Review Charge and Summary Comments

Purpose: To provide independent peer review of an initial draft of this partial report. The peer reviewers were blind to the test agents under study. Introductory materials on RFR and details of the methods dealing with the field generation and animal housing were redacted from the version sent to the reviewers. The reviewers were provided a study data package, also blinded to test agents, containing basic in life study information such as body weight and survival curves and information concerning the generation of pups from the *in utero* exposures.

Report Title: Draft Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Test Articles A and B (and associated Study Data Package)

Reviewers' Names:

David Dorman, D.V.M., Ph.D., North Carolina State University
Russell Cattley, D.V.M., Ph.D., Auburn University
Michael Pino, D.V.M., Ph.D., Pathology consultant

Charge: To peer review the draft report and comment on whether the scientific evidence supports NTP's conclusion(s) for the study findings.

1. Scientific criticisms:
    a. Please comment on whether the information presented in the draft report, including presentation of data in any tables, is clearly and objectively presented. Please suggest any improvements.

    All three reviewers found the results to be clearly and objectively presented, although there were suggestions to provide historical control information for brain and heart lesions for female Harlan Sprague Dawley rats, clarify statements about the specific statistical tests used and the presence or lack of statistical significance of the brain

gliomas in the Results, and expand the conclusions statements to clarify the basis for the conclusions.

b. Please comment on whether NTP's scientific interpretations of the data are objective and reasonable. Please explain why or why not.

The reviewers stated that the NTP had performed an adequate and objective peer review of the pathology data, and the statistical approaches used were consistent with other NTP studies. The methods were described as objective and reasonable. The interpretations of the data, including the limitations, were also reasonable and objective. One reviewer found the data on schwannomas of the heart to be more compelling with respect to an association with treatment than the brain gliomas. This reviewer summarized the findings as:

> "In the heart the evidence for a carcinogenic effect can be based on 1) the presence of the tumors in all six of the test article groups versus none in the controls 2) the statistically significant trend for schwannomas with both compounds and the statistically significant increase in incidence in the 4X (top) dose for test article B; 3) the fact that the incidence of the tumors in both 4X dose groups approaches or exceeds the high end of the historical control range; and 4) the tumors in the 4X group of test article B are accompanied by a higher incidence of Schwann cell hyperplasia. Using the NTP's guide for levels of evidence for carcinogenic activity, I would consider the heart schwannomas as 'Some Evidence' of carcinogenic activity.
>
> The proliferative lesions in the brain are more difficult to interpret because 1) their low incidence that was well within the historical control range, 2) lack of clear dose response; and 3) lack of statistical significance (except for the significant exposure-dependent trend for test article B. . . . However, the presence of malignant gliomas and/or foci of glial cell hyperplasia in 5 of 6 test article groups for both sexes vs none in controls of either sex is suggestive of a test

article effect. . . .I would consider the malignant gliomas as 'Equivocal Evidence' of carcinogenic activity."

2. Please identify any Information that should be added or deleted:

One reviewer suggested that more information be given on the time when tumors were observed (e.g., at terminal necropsy, or early in the study) to help assess the possible impact of the decreased survival times in the control animals on tumor incidence. This reviewer also suggested a discussion of how the survival of control male rats in this study compared to the historical control data. There was also concern that the diagnostic criteria developed by the PWG and used in the current study would impact the historical control incidence rates reported in Table D.

3. The scientific evidence supports NTP's conclusion(s) for the study findings:

The NTP's overall draft conclusion was as follows: "Under the conditions of these studies, the observed hyperplastic lesions and neoplasms outlined in this partial report are considered likely the result of exposures to test article A and test article B. The findings in the heart were statistically stronger than the findings in the brain."

The reviewers had the option of agreeing, agreeing in principle, or disagreeing with the draft conclusions. All three reviewers agreed in principle, reiterating issues discussed above.

APPENDIX G – NIH REVIEWERS' COMMENTS

National Institutes of Health

Peer Review Charge and Reviewers' Comments

Purpose: To provide independent peer review of the pathology diagnoses and statistical evaluation of the partial findings from NTP's studies. Background materials included the draft NTP report, introductory materials on RFR, and details on the methods dealing with the field generation and statistical analyses references and guidance. The reviewers were provided a study data package, containing basic in life study information such as body weight and survival curves, information concerning the generation of pups from the *in utero* exposures, and raw pathology data.

Report Title: Draft Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Test Articles A and B (and associated Study Data Package)

Reviewers' Names:

Diana C. Haines, D.V.M., Frederick National Laboratory
Michael S. Lauer, M.D., Office of Extramural Research, NIH
Maxwell P. Lee, Ph.D., Laboratory of Cancer Biology and Genetics, NCI,
Aleksandra M. Michalowski, M.Sc., Ph.D., Laboratory of Cancer Biology and Genetics, NCI
R. Mark Simpson, D.V.M., Ph.D., Laboratory of Cancer Biology and Genetics, NCI
[Sixth reviewer's name and comments are withheld.]

Charge: To peer review the draft report, statistical analyses, and pathology data and comment on whether the scientific evidence supports NTP's conclusion(s) for the study findings.

Reviewer's comments and NTP responses to the comments are provided.

- Appendix G1: Reviewers' comments
- Appendix G2: NTP's responses to NIH reviewers' comments

Appendix G1: Reviewers' Comments

Reviewer: Diana C. Haines, D.V.M., Frederick National Laboratory

April 5, 2016

Dr. Tabak,

I've always relied on experts, not myself, for statistical analysis, and so do not feel qualified to address the statistical methods used. My training and experience has been in veterinary pathology, including QA review of NTP studies, and serving on PWGs, so will give my opinion on the pathology interpretation (biological significance rather than statistical significance).

Having perused the 3 RFR Draft Report and the raw data, all appears to be in order, including QA of the histopathology (technique) as well as PWG review (diagnosis). Looking at the data, I agree with the report's conclusion: *Under the conditions of these studies, the hyperplastic lesions and neoplasms observed in male rats are considered likely the result of exposures to GSM- and CDMA-modulated RFR. The findings in the heart were statistically stronger than the findings in the brain.* But note, it is "considered likely" not "definitely is".

There may be also several caveats relating to "under the conditions of these studies", including how well the conditions recapitulate actual human exposure: whole body exposure from in utero to old age; 18.5 hours/day (10 min on/10 min off, for total of 9hr actual exposure); and dose[A]. I'm not a physicist, so have to presume experts analyzed and accepted concept of the reverberation chamber, including "doses"[A], as being relevant to human exposure.

[A] Dosimetric Assessment paper: "As could be expected in a study following NTP protocols, the exposure levels for the rodents in this project exceed the limits for the wbSAR and psSAR defined in the IEEE Std C95.1-2005 safety standard for human exposure to mobile phone radiation. In the low dose exposure group the exposure level in the organs exceeds or is close to the localized SAR limit for the general public, except for a few low-water content tissues. More specifically, the psSAR over 1 g in the human head, is limited by the safety standards to <2W/kg, whereas, in the low dose rodents the SAR averaged over the whole brain is >2.4 W/kg for mice, and >1.3 W/kg for rats, hence similar to the limit. Furthermore, the psSAR and oSAR have larger uncertainty compared to the wbSAR. Deviations of the exposure level from the target dose, especially during the early exposure period, should be carefully evaluated in the interpretation of the final biological studies.

Results from the companion mouse study will hopefully add some insight.

Diana Copeland Haines, DVM
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Senior Staff Pathologist, Pathology Section
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Reviewer: Michael S. Lauer, M.D., Office of Extramural Research, NIH

Michael S Lauer, MD (OER)
Review of NTP paper: "Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation (Whole Body Exposures)"
March 20, 2016

Summary of findings:

This is a partial report, a report which is presumably part of a larger set of studies involving 2 species (mice and rats), 2 sexes (male, female), and multiple tissue types, all based on 90-week studies of two different types (GSM and CDMA) of cell phone radiofrequency radiation (RFR). In this partial report, we are given findings regarding brain gliomas and heart schwannomas in male and female Harlan Sprague Dawley rats which were exposed exposed to control or 3 different levels (1.5, 3.0, 6.0) of two types (GSM and CDMA) of RFR. There were 90 rats in each group. Using the poly-3 test with the Bieler-Williams variance adjustment, the authors found a statistically significant increase in the rate of brain gliomas in males exposed to CDMA RFR. Using the poly-6 test, the authors found a statistically significant increase in the rates of heart schwannomas in males exposed to GSM and CDMA. There were no statistically significant differences in rates of gliomas or schwannomas in females; also there was no statistically significant increase in rates of gliomas in males exposed to GSM RFR.

Comments:

1) Why aren't we being told, at least at a high level, of the results of other experiments (i.e., male and female mice, tissues other than heart and brain, tumors other than glioma and schwannoma)? Given the multiple comparisons inherent in this kind of work (see pages 27-30 and Table 13 of the FDA guidance document), there is a high risk of false positive discoveries. In the absence of knowing other findings, we must worry about selective reporting bias.
2) I was able to reproduce the authors' positive P-value findings (see Appendix 1, R code) using the MCPAN R package. However, I'm getting slightly different values for adjusted denominators (also in Appendix 1).
3) I was able to reproduce the authors' findings of longer survival with RFR (see Appendix 1, R code).
4) I have a number of questions about the study design:
    a. Were control rats selected in utero like the exposed rats were?
    b. Were pregnant dams assigned to different groups by formal randomization? If not, why not?
    c. Why were pups in the same litter included? Did the authors take any steps in their analyses to account for the resulting absence of i.i.d?
    d. The authors state that at most 3 pups were chosen per litter. How were the 3 pups chosen (and the others presumably not used for this experiment)? Were the 3 pups that were chosen selected by formal randomization? If not, why not?

   e. Were all analyses based on the intent-to-treat principle? Were there any crossovers? Were all rats accounted for by the end of the experiment and were all rats who started in the experiment included in the final analyses?
   f. Blinding: The authors state that "All PWG reviewer were conducted blinded with respect to treatment group," but in the very next phrase write "only identifying the test articles as 'test agent A' or 'test agent B.'" Why was this information (test agent A or B) given? The blinding was not complete.
5) Sample size:
   a. Did the authors perform a prospective (that is before initiation of the work) sample size calculation? If so, what were the prior assumptions? In other words, why did the authors choose to study 90 rats in each group and why did they set the maximum duration to 90 weeks (instead of 104 weeks)?
   b. I used a publicly available simulation package[1] to calculate the study power for male rats based on the following (see Appendix 2, power calculation simulation studies):
      i. Control tumor rate of ~1.5%.
      ii. Risk ratio 2.5 in the group receiving the highest dose
      iii. 2-sided Alpha = 0.005 (based on Table 13 of the FDA guidance document). Note this low alpha of 0.005 for poly-k trend tests is recommended to minimize the risk of false positive discoveries.
      iv. Sample size of 90 for each group with one planned sacrifice.
      v. Low lethality with lethality parameters set according to study duration and Weibull shape parameter (see Table 3 of Moon et al[1]). When I re-ran the simulations using intermediate lethality, results were not materially changed.
      vi. Study duration 90 weeks
      vii. 5000 simulations
      viii. Note – I used dose levels of 0,1,2, and 4 because I was unable to adjust these on the web site (despite trying 3 different browsers).
   c. Based on these inputs, the recommendations in Table 13 of the FDA guidance document, and a sample size of 90 rats in each group, I find very low power (<5%, see Appendix 2). Even allowing for a risk ratio of 5.0 (a level that is clinically unlikely), the power for 2-sided alpha=0.005, k=3 and low lethality is only ~14% (see Appendix 2).
   d. The low power implies that there is a high risk of false positive findings[2], especially since the epidemiological literature questions the purported association between cell phone exposure and cancer.[3]
6) Summary: I am unable to accept the authors' conclusions:
   a. We need to know all other findings of these experiments (mice, other tumor types) given the risk of false positive findings and reporting bias. It would be helpful to have a copy of the authors' statistical code.
   b. We need to know whether randomization was employed to assign dams to specific groups (control and intervention).

c. We need to know whether randomization was employed to determine which pups from each litter were chosen for continued participation in the experiment.
d. We need to know whether there was a formal power/sample size calculation performed prior to initiation of the experiment. If not, why not? If yes, we need to see the details. In particular, we need to know whether the authors followed the recommendations of the FDA guidance document (in particular Table 13).
e. I suspect that this experiment is substantially underpowered and that the few positive results found reflect false positive findings.[2] The higher survival with RFR, along with the prior epidemiological literature, leaves me even more skeptical of the authors' claims.

References:

1. Moon H, Lee JJ, Ahn H, Nikolova RG. A Web-based Simulator for Sample Size and Power Estimation in Animal Carcinogenicity Studies. *J Stat Software; Vol 1, Issue 13* . 2002. doi:10.18637/jss.v007.i13.
2. Ioannidis JPA. Why most published research findings are false. Jantsch W, Schaffler F, eds. *PLoS Med*. 2005;2(8):e124. doi:10.1371/journal.pmed.0020124.
3. Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ*. 2011;343.

Appendix 1: Attempted replication of positive findings

```
# Review of NTP paper on cell phone RFR and certain cancers
# Attempt to reproduce the positive findings
# Data from Larry Tabak
# Code by Mike Lauer

setwd("~/Desktop/Files to save")

library(MCPAN)
library(rms)
library(Hmisc)

# Read in CDMA NTP data

CDMA <- read.csv("~/Desktop/Files to save/NTP CDMA Raw Tumor Data.csv")

# Survival and treatment group, adjusting for sex, by Cox proportional hazards

CDMA$status<-1
CDMA$S<-Surv(CDMA$Removal.Day, CDMA$status)
f<-cph(S~Treatment+Sex, data=CDMA)
f

# Survival greater (better) for 3.0W, P=0.0157, for 6.0W, P=0.0260

# Table 1 -- Poly-3 test for malignant glioma in males CDMA

males_CDMA<-subset(CDMA, Sex=='M')

poly3test(time=males_CDMA$Removal.Day, status=males_CDMA$Brain.Glioma.Malignant,
        f=males_CDMA$Dose, k=3, type='Williams', method='BW', alternative='greater')

# P=0.039

poly3ci(time=males_CDMA$Removal.Day, status=males_CDMA$Brain.Glioma.Malignant,
        f=males_CDMA$Dose, k=3, type='Williams', method='BW', alternative='greater')

Call result:
```

```
Sample estimates, using poly- 3 -adjustment
                        0         1.5      3      6
x                       0.0000  0.0000  0.0000  3.0000
n                       90.0000 90.0000 90.0000 90.0000
adjusted n              63.8258 72.3688 76.6821 64.8154
adjusted estimate  0.0000  0.0000  0.0000  0.0463

# Table 3 -- Poly-6 test for malignant Schwannoma in males CDMA

poly3test(time=males_CDMA$Removal.Day,
        status=males_CDMA$Heart.Schwannoma.Malignant, f=males_CDMA$Dose, k=6,
        type='Williams', method='BW', alternative='greater')

# P=0.0005

poly3ci(time=males_CDMA$Removal.Day,
        status=males_CDMA$Heart.Schwannoma.Malignant,f=males_CDMA$Dose,
        k=3,type='Williams', method='BW')

Call result:

Sample estimates, using poly- 3 -adjustment
                     0     1.5      3      6
x                 0.0000  2.0000  3.0000  6.0000
n                 90.0000 90.0000 90.0000 90.0000
adjusted n        63.8258 72.3971 77.0575 66.5582
adjusted estimate  0.0000  0.0276  0.0389  0.0901

# Read in GSM NTP data

GSM <- read.csv("~/Desktop/Files to save/NTP GSM Raw Tumor data.csv")

# Survival and treatment group, adjusting for sex, by Cox proportional hazards

GSM$status<-1
GSM$S<-Surv(GSM$Removal.Day, GSM$status)
f<-cph(S~Treatment+Sex, data=GSM)
f

# Survival greater (better) for 6.0W, P=0.0048

males_GSM<-subset(GSM, Sex=='M')

# Table 3 -- Poly-6 test for malignant Schwannomas in males GSM
```

```
poly3test(time=males_GSM$Removal.Day, status=males_GSM$Heart.Schwannoma.Malignant,
        f=males_CDMA$Dose, k=6, type='Williams', method='BW', alternative='greater')

# P=0.004

poly3ci(time=males_GSM$Removal.Day, status=males_GSM$Heart.Schwannoma.Malignant,
        f=males_CDMA$Dose, k=3, type='Williams', method='BW', alternative='greater')
```

Call result:

```
Sample estimates, using poly- 3 -adjustment
                    0     1.5      3      6
x                0.0000  2.0000  1.0000  5.0000
n               90.0000 90.0000 90.0000 90.0000
adjusted n      63.8258 73.1547 76.1127 77.0723
adjusted estimate  0.0000  0.0273  0.0131  0.0649
```

Appendix 2: Simulations for power calculations

Power Simulations for NTP Cell Phone RFR paper (from https://biostatistics.mdanderson.org/acss/Login.aspx and https://www.jstatsoft.org/article/view/v007i13)[1]
Michael Lauer, MD (OER)
March 19, 2016

1) For malignant gliomas (Table 1), P = 0.005, HR = 2.5, k=3

The University of Texas M. D. Anderson Cancer Center
Sample Size and Power Estimation for Animal Carcinogenicity Studies

Reference: "A Web-based Simulator for Sample Size and Power Estimation in Animal Carcinogenicity Studies."
Hojin Moon, J. Jack Lee, Hongshik Ahn and Rumiana G. Nikolova,
Journal of Statistical Software. (2002)[1]

*** Input Parameters ***

Selected Seed = 3000
Number of Groups = 4
Dose metric of each group:
0.00 1.00 2.00 4.00
Number of animals in each group
90 90 90 90
Number of sacrifices including a terminal sacrifice = 1
Sacrifice time points in weeks:

Study duration = 90 weeks
Number of INTERIM sacrificed animals in each interval:
Background tumor onset probability at the end of the study = 0.01
Tumor onset distribution assumed: Weibull with a shape parameter 3.00
Hazard ratio(s) of dose vs. control group
1.50 2.00 2.50
Competing Risks Survival Rate (CRSR) for each group:
0.70 0.70 0.70 0.70
Tumor lethality parameter entered = 23.00
Level of the test = 0.01
One-sided or two-sided test = 2 sided test
Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:
average tumor rate = 0.0149
average competing risks survival rate = 0.6990
average lethality = 0.0816

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0060	0.0000	0.0000
67	0.0002	0.0002	0.0334	0.0000	0.0000
78	0.0003	0.0005	0.0729	0.0000	0.0000
90	0.0005	0.0023	0.1855	0.0094	0.6887

dose group 1:
average tumor rate = 0.0225
average competing risks survival rate = 0.7000
average lethality = 0.0784

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0003	0.0002	0.0325	0.0000	0.0000
78	0.0004	0.0008	0.0720	0.0000	0.0000
90	0.0007	0.0034	0.1851	0.0145	0.6842

dose group 2:
average tumor rate = 0.0297
average competing risks survival rate = 0.6997
average lethality = 0.0772

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0004	0.0003	0.0331	0.0000	0.0000
78	0.0005	0.0012	0.0721	0.0000	0.0000
90	0.0010	0.0045	0.1829	0.0191	0.6790

dose group 3:
average tumor rate = 0.0366
average competing risks survival rate = 0.7007
average lethality = 0.0772

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0005	0.0003	0.0330	0.0000	0.0000

78	0.0006	0.0013	0.0716	0.0000	0.0000
90	0.0012	0.0054	0.1812	0.0238	0.6749

Positive Trend (Power): 0.0238

2) For malignant Schwannomas (Table 3), P = 0.005, HR = 2.5, k=6

The University of Texas M. D. Anderson Cancer Center
Sample Size and Power Estimation for Animal Carcinogenicity Studies

Reference: "A Web-based Simulator for Sample Size and Power
Estimation in Animal Carcinogenicity Studies."
Hojin Moon, J. Jack Lee, Hongshik Ahn and Rumiana G. Nikolova,
Journal of Statistical Software. (2002)[1]

*** Input Parameters ***

Selected Seed = 3000
Number of Groups = 4
Dose metric of each group:
0.00 1.00 2.00 4.00
Number of animals in each group
90 90 90 90
Number of sacrifices including a terminal sacrifice = 1
Sacrifice time points in weeks:

Study duration = 90 weeks
Number of INTERIM sacrificed animals in each interval:
Background tumor onset probability at the end of the study = 0.01
Tumor onset distribution assumed: Weibull with a shape parameter 6.00
Hazard ratio(s) of dose vs. control group
1.50 2.00 2.50
Competing Risks Survival Rate (CRSR) for each group:
0.70 0.70 0.70 0.70
Tumor lethality parameter entered = 45.00
Level of the test = 0.01
One-sided or two-sided test = 2 sided test
Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:
average tumor rate = 0.0149
average competing risks survival rate = 0.6990
average lethality = 0.0631

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0060	0.0000	0.0000
67	0.0001	0.0001	0.0335	0.0000	0.0000
78	0.0002	0.0003	0.0732	0.0000	0.0000
90	0.0005	0.0019	0.1859	0.0096	0.6887

dose group 1:
average tumor rate = 0.0225
average competing risks survival rate = 0.7000
average lethality = 0.0602

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0059	0.0000	0.0000
67	0.0001	0.0001	0.0326	0.0000	0.0000
78	0.0003	0.0005	0.0723	0.0000	0.0000
90	0.0006	0.0029	0.1856	0.0148	0.6842

dose group 2:
average tumor rate = 0.0297
average competing risks survival rate = 0.6997
average lethality = 0.0582

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0059	0.0000	0.0000
67	0.0002	0.0001	0.0333	0.0000	0.0000
78	0.0004	0.0007	0.0726	0.0000	0.0000
90	0.0009	0.0038	0.1837	0.0195	0.6790

dose group 3:
average tumor rate = 0.0366
average competing risks survival rate = 0.7007
average lethality = 0.0588

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0059	0.0000	0.0000
67	0.0003	0.0001	0.0332	0.0000	0.0000
78	0.0005	0.0007	0.0722	0.0000	0.0000
90	0.0011	0.0046	0.1821	0.0243	0.6749

Positive Trend (Power): 0.0230

3) For further consideration, P = 0.005, HR = 5, k=3

The University of Texas M. D. Anderson Cancer Center
Sample Size and Power Estimation for Animal Carcinogenicity Studies

Reference: "A Web-based Simulator for Sample Size and Power
Estimation in Animal Carcinogenicity Studies."
Hojin Moon, J. Jack Lee, Hongshik Ahn and Rumiana G. Nikolova,
Journal of Statistical Software. (2002) In Press.

*** Input Parameters ***

Selected Seed = 3000
Number of Groups = 4
Dose metric of each group:
0.00 1.00 2.00 4.00
Number of animals in each group
90 90 90 90
Number of sacrifices including a terminal sacrifice = 1
Sacrifice time points in weeks:

Study duration = 90 weeks
Number of INTERIM sacrificed animals in each interval:
Background tumor onset probability at the end of the study = 0.01
Tumor onset distribution assumed: Weibull with a shape parameter 3.00
Hazard ratio(s) of dose vs. control group
2.00 3.50 5.00
Competing Risks Survival Rate (CRSR) for each group:
0.70 0.70 0.70 0.70
Tumor lethality parameter entered = 23.00
Level of the test = 0.01
One-sided or two-sided test = 2 sided test
Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:
average tumor rate = 0.0149
average competing risks survival rate = 0.6990

average lethality = 0.0816

sacrifice time	d	a1	b1	a2	b2
45	0.0000	0.0000	0.0060	0.0000	0.0000
67	0.0002	0.0002	0.0334	0.0000	0.0000
78	0.0003	0.0005	0.0729	0.0000	0.0000
90	0.0005	0.0023	0.1855	0.0094	0.6887

dose group 1:
average tumor rate = 0.0301
average competing risks survival rate = 0.7000
average lethality = 0.0743

sacrifice time	d	a1	b1	a2	b2
45	0.0001	0.0000	0.0059	0.0000	0.0000
67	0.0004	0.0003	0.0324	0.0000	0.0000
78	0.0005	0.0011	0.0717	0.0000	0.0000
90	0.0009	0.0045	0.1839	0.0194	0.6789

dose group 2:
average tumor rate = 0.0515
average competing risks survival rate = 0.6997
average lethality = 0.0774

sacrifice time	d	a1	b1	a2	b2
45	0.0002	0.0000	0.0058	0.0000	0.0000
67	0.0007	0.0006	0.0328	0.0000	0.0000
78	0.0009	0.0020	0.0713	0.0000	0.0000
90	0.0017	0.0076	0.1795	0.0331	0.6638

dose group 3:
average tumor rate = 0.0727
average competing risks survival rate = 0.7007
average lethality = 0.0804

sacrifice time	d	a1	b1	a2	b2
45	0.0003	0.0000	0.0059	0.0000	0.0000
67	0.0010	0.0006	0.0327	0.0000	0.0000
78	0.0013	0.0028	0.0701	0.0000	0.0000
90	0.0025	0.0107	0.1755	0.0470	0.6496

Positive Trend (Power): 0.1420

4) For further consideration, same as in baseline (1) but with intermediate lethality

*** Input Parameters ***

Selected Seed = 3000
Number of Groups = 4
Dose metric of each group:
0.00 1.00 2.00 4.00
Number of animals in each group
90 90 90 90
Number of sacrifices including a terminal sacrifice = 1
Sacrifice time points in weeks:

Study duration = 90 weeks
Number of INTERIM sacrificed animals in each interval:
Background tumor onset probability at the end of the study = 0.01
Tumor onset distribution assumed: Weibull with a shape parameter 3.00
Hazard ratio(s) of dose vs. control group
1.50 2.00 2.50
Competing Risks Survival Rate (CRSR) for each group:
0.70 0.70 0.70 0.70
Tumor lethality parameter entered = 225.00
Level of the test = 0.01
One-sided or two-sided test = 2 sided test
Number of simulation runs = 5000

*** Simulation Results ***

dose group 0:
average tumor rate = 0.0149
average competing risks survival rate = 0.6990
average lethality = 0.3936

sacrifice time	d	a1	b1	a2	b2
45	0.0004	0.0000	0.0060	0.0000	0.0000
67	0.0014	0.0001	0.0334	0.0000	0.0000
78	0.0014	0.0004	0.0729	0.0000	0.0000
90	0.0019	0.0015	0.1855	0.0063	0.6887

dose group 1:
average tumor rate = 0.0225
average competing risks survival rate = 0.7000
average lethality = 0.3852

sacrifice time	d	a1	b1	a2	b2
45	0.0006	0.0000	0.0059	0.0000	0.0000
67	0.0022	0.0001	0.0325	0.0000	0.0000
78	0.0020	0.0006	0.0720	0.0000	0.0000
90	0.0029	0.0023	0.1851	0.0097	0.6842

dose group 2:
average tumor rate = 0.0297
average competing risks survival rate = 0.6997
average lethality = 0.3839

sacrifice time	d	a1	b1	a2	b2
45	0.0008	0.0000	0.0059	0.0000	0.0000
67	0.0029	0.0003	0.0331	0.0000	0.0000
78	0.0027	0.0008	0.0721	0.0000	0.0000
90	0.0039	0.0031	0.1829	0.0127	0.6790

dose group 3:
average tumor rate = 0.0366
average competing risks survival rate = 0.7007
average lethality = 0.3897

sacrifice time	d	a1	b1	a2	b2
45	0.0009	0.0000	0.0059	0.0000	0.0000
67	0.0037	0.0003	0.0330	0.0000	0.0000
78	0.0033	0.0009	0.0716	0.0000	0.0000
90	0.0048	0.0037	0.1812	0.0157	0.6749

Positive Trend (Power): 0.0219

References:

1. Moon H, Lee JJ, Ahn H, Nikolova RG. A Web-based Simulator for Sample Size and Power Estimation in Animal Carcinogenicity Studies. *J Stat Software; Vol 1, Issue 13* . 2002. doi:10.18637/jss.v007.i13.
2. Ioannidis JPA. Why most published research findings are false. Jantsch W, Schaffler F, eds. *PLoS Med*. 2005;2(8):e124. doi:10.1371/journal.pmed.0020124.
3. Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ*. 2011;343.

Reviewer: Maxwell P. Lee, Ph.D., Laboratory of Cancer Biology and Genetics, NCI

I think the study was well designed and the analyses and results were clearly presented.

My main concern is the control data. Since the main finding was the increased incidence rates of heart schwannomas and brain gliomas in male Harlan Sprague Dawley rats exposed to GSM- or CDMA-modulated cell phone RFR, my analyses and evaluation below were focused on the male rats.

My concern regarding the control data came from the following two considerations. First, we need to consider sample variation. The incidence rates of the current controls for brain gliomas and heart schwannomas were 0. However, the historical controls were 1.67% for gliomas (range 0-8%) and 1.30% for schwannomas (0-6%). Given that there were substantial variations among the historical controls and the concurrent control is at the lowest end of the range, it is important to evaluate how different estimates of control incidence rates may impact the results of analyses. Supplementary Table S1 shows that for gliomas with 1.7% incidence rate we have 40%, 37%, 17%, and 6% of chance to observe 0 tumor, 1 tumor, 2 tumors, and greater than 2 tumors, respectively; heart schwannomas has similar distribution. Given the low incidence rate and moderate sample size of the control, even after observing 0 tumor in the current study, the 'true' incidence rate may be higher than 0. If we were repeating the experiment, we may see some control studies have 1 or more tumors. Second, it is puzzling why the control had short survival rate. Given that most of the gliomas and heart schwannomas are late-developing tumors, it is possible that if the controls were living longer some tumors might develop. Although the use of poly-3 (or poly-6) test intended to adjust the number of rats used in the study, it is still important to re-evaluate the analysis by considering the incidence rate in controls not being 0.

Therefore, I have performed the analyses using the original data as well as the data modified by adding 1 tumor to the control. I implemented the poly-3 (or poly-6) trend test in R using the formula described in the file, Poly3 correction factor[1].docx.

The results are summarized in Table 1 for brain gliomas.

Table 1. Incidence of brain gliomas in male rats exposed to GSM- or CDMA-modulated RFR, comparing control data with 0 vs. 1 tumor.

RFR	W/kg				pvalue
	0	1.5	3	6	
GSM	0	3	3	2	0.9771
GSM	1	3	3	2	0.8668
CDMA	0	0	0	3	0.0233
CDMA	1	0	0	3	0.1077

Poly-6 adjusted rates were used in the chi-square trend test. The 1^{st} and 3^{rd} rows correspond to the original data with 0 tumor observed in the control group (The numbers in Table 1 here are identical to those in Table 1 in the original report). The test is significant for CDMA exposures (pvalue = 0.0233). However, it is not significant after adding 1 tumor to the control group (pvalue = 0.1077, the 4^{th} row).

Similar analysis was performed for heart schwannomas. The results are summarized in Table 2.

Table 2. Incidence of heart schwannomas in male rats exposed to GSM- or CDMA-modulated RFR, comparing control data with 0 vs. 1 tumor.

RFR	W/kg				pvalue
	0	1.5	3	6	
GSM	0	2	1	5	0.0431
GSM	1	2	1	5	0.1079
CDMA	0	2	3	6	0.0144
CDMA	1	2	3	6	0.0365

Poly-3 adjusted rates were used in the chi-square trend test. The 1^{st} and 3^{rd} rows correspond to the original data with 0 tumor observed in the control group (The numbers in Table 2 here are identical to those in Table 3 in the original report). The tests are significant for both GSM (pvalue = 0.0431) and CDMA (pvalue = 0.0144) exposures. However, only CDMA exposure remains significant after adding 1 tumor to the control group (pvalue = 0.0365, the 4^{th} row).

Since the incidence of heart schwannomas in the 6 W/kg males was significantly higher in CDMA exposed males than the control group in the original report, I also analyzed the impact of adding 1 tumor to the control group.

Table 3. Incidence of heart schwannomas in male rats exposed to 6 W/kg CDMA-modulated RFR, comparing control data with 0 vs. 1 tumor.

RFR	W/kg		pvalue
	0	6	
CDMA	0	6	0.0381
CDMA	1	6	0.0986

Poly-3 adjusted rates were used in the chi-square trend test. The 1^{st} row corresponds to the original data with 0 tumor observed in the control group. The test was significant for CDMA exposures (pvalue = 0.0381). However, it was not significant after adding 1 tumor to the control group (pvalue = 0.0986, the 2^{nd} row).

Conclusions

Increased incidence of heart schwannomas in male rats exposed to GSM- or CDMA-modulated RFR is statistically significant by the chi-square trend test. The evidence is better for CDMA exposure than GSM exposure. I think additional experiments are needed to assess if the incidence of brain gliomas in male rats exposed to GSM- or CDMA-modulated RFR is significantly higher than the control group or not.

My additional comments are summarized below.

1. I compared poly-3 adjusted number from Table 3 in the original report versus the poly-3 adjusted number that I calculated using the raw data from the excel files. Supplementary Figure S1 shows that these two sets of numbers agree with each other in general. This is in contrast to the comparison for poly-6 adjusted number from Table 1 in the original report versus the poly-6 adjusted number that I calculated using the raw data from the excel files (Supplementary Figure S2). In fact, the adjusted rat numbers from Table 1 and Table 3 of the original report look quite similar (Supplementary Figure S3). This suggests that the poly-3 adjusted number was used in the footnotes in both Table 1 and Table 3 in the original report.

2. I noted that in Table S2 the adjusted numbers in from.original.report and poly3 are identical at Dose 0 and 1.5 for both CDMA and GSM as well as at Dose 3 for GSM but differ slightly in the other treatment doses for heart schwannomas. One possible cause of the difference is that the version of the raw data in the excel files differs from that used to generate the original report. The second possibility is typo in the footnote in Table 3. I also generated Table S3 that has the poly-6 adjusted numbers for brain gliomas. The two sets of the poly-6 adjusted numbers are very different.

3. There are a couple of errors in the footnote of Table 3 in the original report. 2/74.05 (5%) should be 2/74.05 (2.7%). 3/78.67 (4%) should be 3/78.67 (3.8%).

Supplementary Information

Table S1. Expected percentage of observing different numbers of tumors in the controls based on binomial distribution.

	0 tumor	1 tumor	2 tumors	>2 tumors
control for glioma	40%	37%	17%	6%
control for heart schwannoma	43%	37%	15%	5%

The percentage was calculated with 1.7% historical control rate for male rats (gliomas) and with poly-6 adjusted animal number, 53. Similarly, the percentage was calculated with 1.3% historical control rate for male (heart schwannoma) and with poly-3 adjusted animal number, 65.

Table S2. The poly-3 adjusted rat numbers in Table 3 in the original report and those calculated from the raw data.

RFR	Dose	from.original.report	poly3
CDMA	0	65.47	65.47
CDMA	1.5	74.05	74.05
CDMA	3	78.67	78.35
CDMA	6	67.94	66.24
GSM	0	65.47	65.47
GSM	1.5	74.87	74.87
GSM	3	77.89	77.89
GSM	6	78.48	77.66

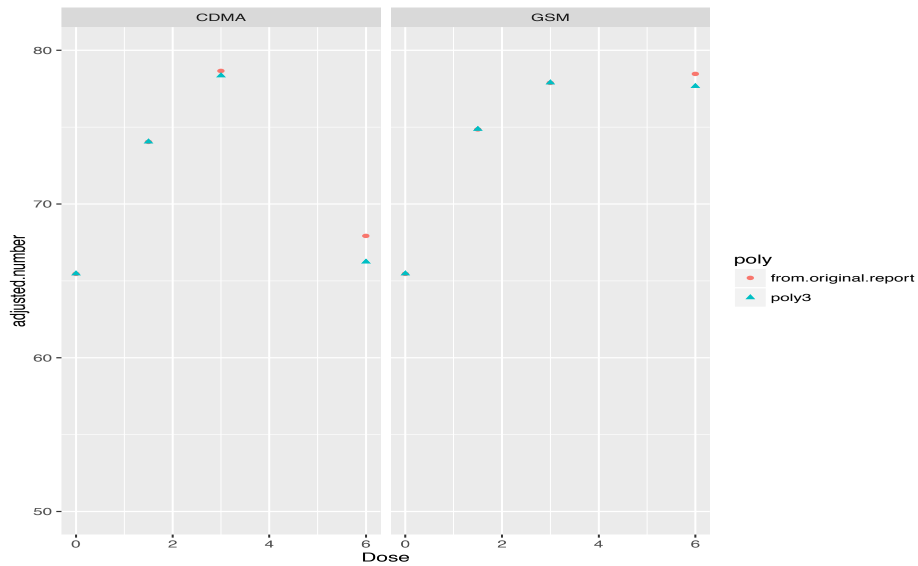
The numbers in from.original.report refers to the poly-3 adjusted rat number from Table 3 in the original report. The numbers in poly3 refers to the poly-3 adjusted rat numbers that I calculated from the raw data for heart schwannoma.

Table S3. The poly-6 adjusted rat numbers in Table 1 in the original report and those calculated from the raw data.

RFR	Dose	from.original.report	poly6
CDMA	0	65.47	53.48
CDMA	1.5	74.05	65.94
CDMA	3	78.35	73.08
CDMA	6	66.24	57.5
GSM	0	65.47	53.48
GSM	1.5	74.93	67.84
GSM	3	78.27	71.43
GSM	6	77.1	72.55

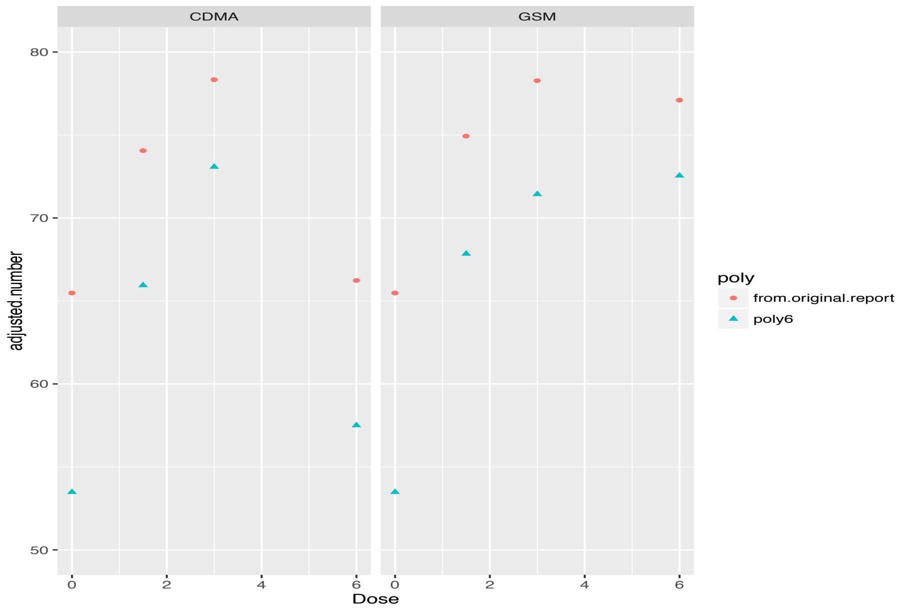
The numbers in from.original.report refers to the poly-6 adjusted rat number from Table 1 in the original report. The numbers in poly6 refers to the poly-6 adjusted rat numbers that I calculated from the raw data for brain gliomas.

Figure S1. Comparison of poly-3 adjusted rat numbers between those from the original report versus those calculated from the raw data.



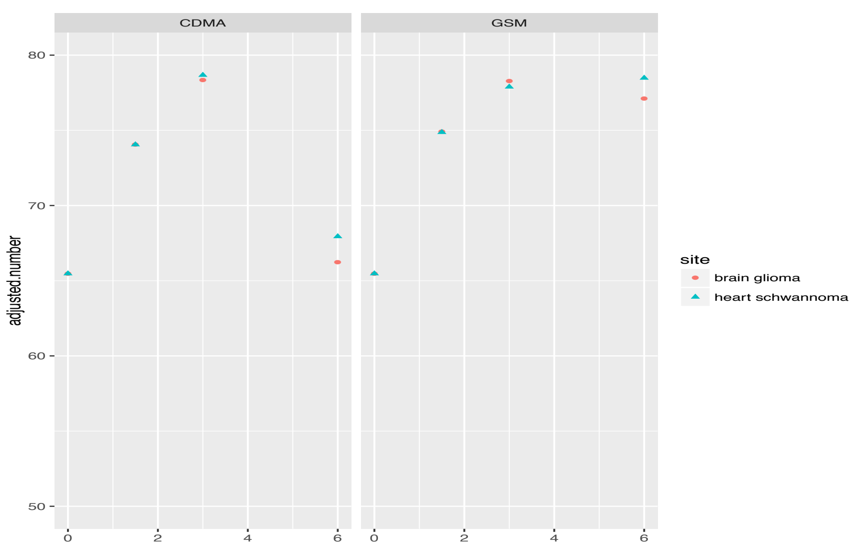
The poly-3 adjusted rat number from Table 3 of the original report is compared with the poly-3 adjusted rat number that I calculated from the raw data for heart schwannomas experiment.

Figure S2. Comparison of poly-6 adjusted rat numbers between those from the original report versus those calculated from the raw data.



The poly-6 adjusted rat number from Table 1 of the original report is compared with the poly-6 adjusted rat number that I calculated from the raw data for brain gliomas experiment.

Figure S3. Comparison of poly-6 adjusted rat numbers between those from the original report versus those calculated from the raw data.



The adjusted rat numbers from Table 1 and Table 3 of the original report are compared with each other.

Reviewer: Aleksandra M. Michalowski, M.Sc., Ph.D., Laboratory of Cancer Biology and Genetics, NCI

REVIEWER COMMENTS

Reviewer's Name:
Aleksandra M. Michalowski, Ph.D., M.Sc., National Cancer Institute/LCBG

Report Title:
Report of Partial Findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation (Whole Body Exposures); Draft 3-16-2016

Charge: To peer review the draft report and comment on whether the scientific evidence supports NTP's conclusion(s) for the study findings.

1. Scientific criticisms:

   a. *Please comment on whether the information presented in the draft report, including presentation of data in any tables, is clearly and objectively presented. Please suggest any improvements.*

      Overall, the information included in the report is presented in a comprehensive and accurate manner. Specifically, the experimental design and conditions are sufficiently documented and the choice of statistical approaches is explained; the results are well organized and necessary details are provided.

      Nevertheless, a few additions could be suggested:

      (1) Appendix tables for all poly-k tests performed could be added. I believe this would enhance the presentation of the adjusted rates and the strength of the statistical evidence. As a possible example I prepared the below table using the R package *MCPAN* and its *poly3test()* function.

poly-3	Heart Schwannoma Malignant, Male				Heart Schwannoma Malignant, Female			
CDMA exposure	0	1.5	3	6	0	1.5	3	6
X	0	2	3	6	0	2	0	2
N	90	90	90	90	90	90	90	90
adjusted n	63.8	72.4	77.1	66.6	67.9	71.8	70.3	78.0
Dunnett contrast	–	1.5 - 0	3 - 0	6 - 0	–	1.5 - 0	3 - 0	6 - 0
Estimate	0	0.03	0.04	0.09	0	0.03	0	0.03
Statistic	–	1.24	1.58	2.45	–	1.26	0	1.24
p-value	–	0.2704	0.1542	**0.0209**	–	0.2466	0.7992	0.2562
Williams contrast	–	(6,3,1.5) - 0	(6,3) - 0	6 - 0	–	(6,3,1.5) - 0	(6,3) - 0	6 - 0
Estimate	0	0.05	0.06	0.09	0	0.02	0.01	0.03
Statistic	–	2.78	2.75	2.45	–	1.27	0.88	1.24
p-value	–	**0.0056**	**0.0060**	**0.0138**	–	0.1661	0.2871	0.1744

      (2) In the portion of the text describing poly-k test results, p-values are given for significant pairwise comparisons; I would also give the p-values estimated for the significant trends (maximum test).

(3) Information could be included regarding the software or programming environment used for the computations.

(4) In the portion of the text describing differences in survival at the end of the study between control and RFR-exposed animals (page 5§2) the compared characteristic is not named (median survival, TSAC?) and also no numerical values of the estimates or the range of differences are given. I would add numbers in the text or an Appendix table showing the group survival estimates described in this paragraph.

Median survival

CDMA	Female	Male	GSM	Female	Male
0	737	662.5	0	737	662.5
1.5	734	719	1.50	738	729
3	737	731	3	737	730
6	738.5	717	6	738	731

TSAC percentage

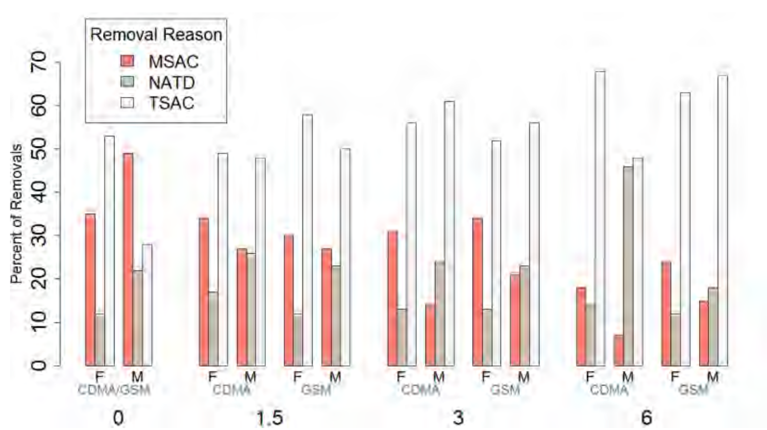
CDMA	Female	Male	GSM	Female	Male
0	53	28	0	53	28
1.5	49	48	1.5	58	50
3	56	61	3	52	56
6	68	48	6	63	67

b. *Please comment on whether NTP's scientific interpretations of the data are objective and reasonable. Please explain why or why not.*

Appropriate statistical design and methods were applied in accord with the FDA/NTP guidelines for conducting long-term rodent carcinogenicity studies and analyses. The results and limiting issues were objectively discussed. The critical issue of shorter survival in the male control group was addressed with regard to the percentage of animals surviving to terminal sacrifice in historical control data (avg. 47%, range 24% to 72%) and the possible impact of the observed age of tumor occurrence on the statistical inference.

I believe detailed information about animal selection and randomization procedures should be given so that the potential for allocation bias could be judged. As shown in the figure below, the lower survival rate to terminal sacrifice (28%) in the male control is accompanied by the higher rate of moribund sacrifice (49%); in the male group exposed to CDMA with 6 W/kg, a higher rate of natural death was observed (46%).

It has been reported that insufficient randomization can lead to differences in survival rates. As an example, in a carcinogenicity study on aspartame it was suggested that lack of randomization to different rooms may have possibly been the cause of low survival rates (27%) in the control female group due to a high background infection rate (EFSA, 2006; Magnuson, B., Williams, G.M., 2008).



2. Please identify any information that should be added or deleted:

A statement of the required statistical significance level should be added. FDA guidance suggests the use of significance levels of 0.025 and 0.005 for tests for positive trends in incidence rates of rare tumors and common tumors, respectively; for testing pairwise differences in tumor incidence the use of significance levels of 0.05 and 0.01 is recommended for rare and common tumors, respectively. If power calculations to determine the required sample size were performed, the results should also be included.

3. The scientific evidence supports NTP's conclusion(s) for the study findings:

The NTP's overall draft conclusion was as follows: "Under the conditions of these studies, the observed hyperplastic lesions and neoplasms outlined in this partial report are considered likely the result of exposures to test article A and test article B. The findings in the heart were statistically stronger than the findings in the brain."

In my view, the results support the conclusion of likely carcinogenic effect of the RFR-exposure on Schwannoma heart lesions in male Harlan Sprague Dawley rats.

Possible carcinogenic effects in the brain are marginal and are not sufficiently supported by statistical evidence in the male Harlan Sprague Dawley rats.

In the female Harlan Sprague Dawley rats very few lesions were observed in either site and statistical significance was not reached at all.

Reviewer: R. Mark Simpson, D.V.M., Ph.D., Laboratory of Cancer Biology and Genetics, NCI

Analysis of National Toxicology Program (NTP) study evaluating risk in rat lifetime exposure to GSM or CDMA RFR.

Notes:

The NTP study document acknowledges several study limitations [page 10, discussion section]. Potential limitations should prominently factor into considerations regarding the context of the findings, as well as their interpretation and application.

<u>Working list of limitations potentially impacting NTP study interpretations</u>

- Difficulty in achieving diagnostic consensus in lesions classifications of rare, unusual, and incompletely understood lesion association
- Document appears to indicate that the second Pathology Working Group (PWG) empaneled to review and obtain lesion classification consensus, following the inability of the initial PWG to do so, may have reviewed different lesions sets
- No record of clinical disease manifestations due to lesions involving heart and brain [note lesions in heart and brain are mutually exclusive; affected rats have either one or the other and do not appear to have the involvement of both organs together (appendix E)]
- Lesions, including malignancies, do not appear to materially shorten lifespan, except for a subgroup of rats (less than 1/3 of affected rats) with malignant Schwannomas in heart
- Lack of shortened lifespan as a consequence of malignancy for the majority of affected rats contrasts with shortened lifespan of male control rats for which there is absence of attributable cause of death. The survival of the control group of male rats in the current study (28%) was relatively low compared to other recent NTP studies (avg 47%, range 24 to 72%).
  Creates greater reliance on statistical controlling for survival disparities and reliance on historical controls
- Reliance on historical controls made up of rats of different genetic strain background, held under different environmental conditions
- Absence of data on incidence of more frequently expected tumor occurrences in rats (background lesions)

Documenting the nature of the brain and cardiac lesions observed in RFR exposed rats and placing them into test article exposure-related context, in contrast to potential for their occurring spontaneously, are important and challenging goals. The NTP study limitations make the interpretation of reasonable risk more complicated. NTP acknowledgements of study limitations appear factored into one of NTP's reviewer's study conclusion, i.e., findings represent "some evidence" for a test article effect in statistically significant trend for Schwannomas; an opinion which is coupled with a conclusion for "equivocal evidence" of an effect in relation to malignant gliomas of the brain [NTP Appendix F, Reviewer Comments].

The summation from Appendix F reviewers regarding existence of test article effect is less than conclusive. The NTP study documents a series of cytoproliferative changes

in heart and brain. The nature of some of the changes is challenging diagnostically and appears to be incompletely understood. These findings are presented in the absence of complete analysis of the entire consequences of the study effects. For example, no potential significance for test article effect context is given to any of granular cell proliferative lesions of the brain, a finding mentioned only as a contrast to what was less well understood pathologically (NTP Appendix C, Pathology). It is noteworthy that the lesion types analyzed in the NTP RFR study under review are uncommon historically in rats, in the organs discussed. Furthermore, the malignancies of neuroglia appear to be paired with the occurrence of poorly understood changes involving neuroglial cell hyperplasias in the central and peripheral nervous systems. Little information can be gleaned from the literature about the nature and significance of these latter proliferative changes, interpreted by NTP as nonneoplastic and non-inflammation-reactive neuroglial cell in nature. Although unclear in the NTP study document, it is plausible that the particular lesion constellation, along with the relative novelty of some lesions, contributed to the lack of consensus regarding the nature of the lesions on the part of the initial PWG study pathologists. Concern raised by one of the reviewers (Appendix F, Reviewer Comments) regarding how this difficulty in ability to classify lesions might impact comparisons to historical control lesion incidence data (NTP Table D) is certainly principled.

The extraordinary PWG process, presumably posed by the difficult diagnostic interpretations, has the potential to influence the reliance on historical controls. In this regard, study limitations concerning determination of whether or not there is a test article effect include the substantially poor survival of male rats in the control group. The survival of the control group of male rats in the study under review (28%) was relatively low compared to other recent NTP studies (avg 47%, range 24 to 72%). This apparently led to greater statistical construction to account for the impact of study matched controls, and created increased reliance upon historical data of rare tumor incidences in control animals taken from other chronic carcinogenicity studies. NTP acknowledges a limitation in using the historical incident data and a small study match control group due to poor survivability. There are potential sources of variability when using historical controls of different rat strains and fluctuating study conditions (environment, vehicle, route of exposure, etc.), as is the case here. It seems less than clear what appropriate background lesion incidence is, as NTP indicates some data involve other strains of rats. The range of lesion incidence in historical controls could mean that the true incidence of some lesions varies considerably and might be considered rare or more common depending upon the incidence rate.

The guidance manual on Statistical Aspects of the Design, Analysis and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals by the FDA provided for this review discusses applying comparisons using historical control lesion incidences at some length [beginning page 27, line 996]. Considering lesions as being rare or more common appears to influence selection of the level of statistical significance for comparisons. It appears that analysis for significant differences in tumor incidence between the control and the dose groups for these NTP studies has been established at the 0.05 level (NTP Tables 1,3,5). Interpretations of trend tests may be influenced by the choice of decision rule applied. Such choices can result in

about twice as large overall false positive error as that associated with control-high pairwise comparison tests [page 28, line 1012-1026]. The FDA guidance manual [page 31, line 1136] highlights concern regarding reliance upon historical control incidence data, stating that using historical control data in the interpretation of statistical test results is not very satisfactory because the range of historical control rates is usually too wide. This is especially true in situations in which the historical tumor rates of most studies used are clustered together, but a few other studies give rates far away from the cluster. When the range of historical control data is simply calculated as the difference between the maximum and the minimum of the historical control rates, the range does not consider the shape of the distribution of the rates. These circumstances may impose some limitations on optimal risk assessment designs.

Somewhat paradoxically then, NTP study limitations including that imposed due to reliance upon less than optimal historical control lesion incidence data for much of the comparisons between treated and untreated rats, is confronted by existence of a difficult to classify and incompletely understood lesion constellation interpreted to include neuroglial cell hyperplasia. Notwithstanding, this confounding proliferative lesion occurring in the context along with malignancies of apparently similar histogeneses, sustains a level of concern for a rare injury mechanism related to test article effect. Additional information about the study together with an assessment of the statistical analyses may enhance the value of this analysis.

R. Mark Simpson, D.V.M., Ph.D.

Appendix G2: NTP's Responses to NIH Reviewers' Comments

NTP Responses to Pathology Reviewers' Comments April 12, 2016

Reviewers: R. Mark Simpson, D.V.M., Ph.D. and Diana Copeland Haines, D.V.M.

Responses Relating to the Pathology Review Process

Drafts of the PWG reports are provided. As described in the PWG report, the specific task of the first PWG (January 29th, 2016) was to: 1) confirm the presence of glial cell hyperplasia and malignant gliomas in the brain and Schwann cell hyperplasia and schwannomas in the heart; 2) develop specific diagnostic criteria in the brain for distinguishing glial cell hyperplasia from malignant glioma and gliosis, and in the heart for distinguishing between Schwann cell hyperplasia and schwannoma. The PWG participants confirmed the malignant gliomas and schwannomas, but the criteria for distinguishing between hyperplasia and neoplasia differed between the participants.

In order to clearly establish specific diagnostic criteria for the differentiation between hyperplastic and neoplastic lesions in the brain and heart, two additional PWGs were convened. The participants for the second (February 25, 2016) and third (March 3, 2016) PWGs were selected based on their distinguished expertise in the fields of neuropathology and cardiovascular pathology, respectively. Some of the participants were leaders in the International Harmonization of Nomenclature and Diagnostic Criteria initiative. The neuropathology experts of the second PWG confirmed the malignant gliomas in the brain, established diagnostic criteria for glial cell hyperplasia, and agreed that the hyperplastic lesions are within a continuum leading to malignant glioma. The cardiovascular pathology experts of the third PWG established specific diagnostic criteria for Schwann cell hyperplasia and schwannoma in the endocardium and myocardium, and reviewed and confirmed all cases of Schwann cell hyperplasia and schwannoma observed in these studies. The outcome of the PWG provided a very high degree of confidence in the diagnoses.

The participants of the first PWG (January 29th, 2016) only reviewed a subset of the glial lesions that were observed in the studies. The review for the second PWG (February 25, 2016) included all glial lesions in the studies including the subset that was reviewed in the first PWG.

Responses Relating to Considerations of Historical Control Data

For NTP toxicology and carcinogenicity studies, the concurrent controls are always the primary comparison group. However, historical control information is useful particularly in instances when there is differential survival between controls and exposed groups, as was observed in the RFR studies. Rates for glial cell neoplasms and heart schwannomas from control groups of male Harlan Sprague Dawley rats from other recently completed NTP studies are presented in Appendix D of the 3-16-2016 draft report. While Harlan Sprague Dawley rats are an outbred strain, they are considered a single genetic strain in the same sense as other outbred strains, such as the Long-Evans or Wistar rat. Therefore, these historical control tumor rates are applicable to this study. However, it's important to note that the studies listed in Appendix D were carried out at laboratories other than the RFR studies, and under different housing and environmental conditions. At the time of the 3-16-2016 draft report, not all of these studies had undergone a complete pathology peer review. In the past several weeks NTP pathologists have reviewed brain and heart slides from these male rat control groups, and have confirmed, with few exceptions, the low rates of hyperplastic and neoplastic lesions reported in Appendix D, applying the diagnostic criteria established during the PWGs outlined in Appendix C.

NTP Comments on Statistical Issues Raised by the Reviewers April 12, 2016

Given the multiple comparisons inherent in this kind of work, there is a high risk of false positive discoveries (Michael S. Lauer).

Although the NTP conducts statistical tests on multiple cancer endpoints in any given study, numerous authors have shown that the study-wide false positive rate does not greatly exceed 0.05 (Fears et al., 1977; Haseman, 1983; Office of Science and Technology Policy, 1985; Haseman, 1990; Haseman and Elwell, 1996; Lin and Rahman, 1998; Rahman and Lin, 2008; Kissling et al., 2014). One reason for this is that NTP's carcinogenicity decisions are not based solely on statistics and in many instances statistically significant findings are not concluded to be due to the test agent. Many factors go into this determination including whether there were pre-neoplastic lesions, whether there was a dose-response relationship, biological plausibility, background rates and variability of the tumor, etc. Additionally, with rare tumors especially, the actual false positive rate of each individual test is well below 0.05, due to the discrete nature of the data, so the cumulative false positive rate from many such tests is less than a person would expect by multiplying 0.05 by the number of tests conducted (Fears et al., 1977; Haseman, 1983; Kissling et al., 2015).

I'm getting slightly different values for poly-k adjusted denominators (Michael S. Lauer).

I compared poly---3 adjusted number from Table 3 in the original report versus the poly---3 adjusted number that I calculated using the raw data from the excel files. Supplementary Figure S1 shows that these two sets of numbers agree with each other in general. This is in contrast to the comparison for poly---6 adjusted number from Table 1 in the original report versus the poly---6 adjusted number that I calculated using the raw data from the excel files (Supplementary Figure S2). In fact, the adjusted rat numbers from Table 1 and Table 3 of the original report look quite similar (Supplementary Figure S3). This suggests that the poly---3 adjusted number was used in the footnotes in both Table 1 and Table 3 in the original report. (Max Lee)

I noted that in Table S2 the adjusted numbers in from.original.report and poly3 are identical at Dose 0 and 1.5 for both CDMA and GSM as well as at Dose 3 for GSM but differ slightly in the other treatment doses for heart schwannomas. One possible cause of the difference is that the version of the raw data in the excel files differs from that used to generate the original report. The second possibility is typo in the footnote in Table 3. I also generated Table S3 that has the poly---6 adjusted numbers for brain gliomas. The two sets of the poly---6 adjusted numbers are very different. (Max Lee)

Information could be included regarding the software or programming environment used for the computations. (Aleksandra M. Michalowski)

The adjusted denominators in Table 1 of the original report were labeled as poly-6 denominators, but were actually poly-3 denominators. This error was noted and brought to Dr Tabak's attention by Dr. Bucher in a March 22 email.

The p-values and adjusted denominators calculated by NTP are correct, except as noted for Table 1, and were calculated using validated poly-k software. This software is coded in Java and is embedded within NTP's TDMSE (Toxicology Data Management System Enterprise) system. Poly-k

calculations conducted by the reviewers in R may vary slightly from the NTP's calculation due to selection of study length and the NTP's use of the Bieler-Williams variance adjustment and a continuity correction. In his calculations, Dr. Lauer used 90 weeks as the study length, whereas the actual study length was 104 weeks. It is not apparent from the R documentation that the Bieler-Williams adjustment or the continuity correction is incorporated into the poly-3 calculations in R. In his calculations, Dr. Lee used two-sided p-values. In NTP statistical tests for carcinogenicity, the expectation is that if the test article is carcinogenic, tumor rates should increase with increasing exposure; thus, the NTP employs one-sided tests and p-values are one-sided. Using one-sided p-values in Dr. Lee's Table 1, the GSM trend if there were 1 brain glioma in the control group remains nonsignificant, but the CDMA trend approaches 0.05 (p = 0.054) if there were 1 brain glioma in the control group. In Dr. Lee's Table 2, the one-sided p-value for the GSM trend if there were 1 heart schwannoma in the control group approaches 0.05 (p = 0.054) and the one-sided p-value for the CDMA trend in heart schwannomas remains significant at p = 0.018 if there were 1 heart schwannoma in the control group. In Dr. Lee's Table 3, the one-sided p-value for the CDMA pairwise comparison is significant at p = 0.049 if there were 1 heart schwannoma in the control group.

A statement of the required statistical significance level should be added. FDA guidance suggests the use of significance levels of 0.025 and 0.005 for tests for positive trends in incidence rates of rare tumors and common tumors, respectively; for testing pairwise differences in tumor incidence the use of significance levels of 0.05 and 0.01 is recommended for rare and common tumors, respectively. (Aleksandra M. Michalowski)

Although the FDA guidance suggests lowering the significance level for most tests of trend and pairwise differences, this guidance is based on a misunderstanding of findings reported by Haseman (1983). In this paper, Haseman discusses several rules proposed by others for setting the significance level lower than 0.05. *If* these rules are rigidly followed, Haseman showed that study conclusions will be consistent with the NTP's more complex decision-making process, for which 0.05 is the nominal significance level and p-values are taken into consideration along with other factors (outlined above in response to comment 1) in determining whether the tumor increase is biologically significant. The NTP does not strictly adhere to a specific statistical significance level in determining whether a carcinogenic effect is present.

Appendix tables for all poly-k tests performed could be added. (Aleksandra M. Michalowski)

Dr. Michalowski proposed a sample table. The rows corresponding to X, N, adjusted n are already included in the tables or appear the footnotes in the tables. The rows corresponding to "Dunnett contrast" and "Williams contrast" are not appropriate for dichotomous tumor data. Both Dunnett's test and Williams' test assume that the data are continuous and normally distributed.

In the portion of the text describing poly-k test results, p-values are given for significant pairwise comparisons; I would also give the p-values estimated for the significant trends. (Aleksandra M. Michalowski)

Indicators of significant trends are given in the tables in the form of asterisks next to control group tumor counts.

There are a couple of errors in the footnote of Table 3 in the original report. 2/74.05 (5%) should be 2/74.05 (2.7%). 3/78.67 (4%) should be 3/78.67 (3.8%). (Max Lee)

Thank you for pointing this out. The percentages will be corrected in our final report.

Were control rats selected in utero like the exposed rats were? Were pregnant dams assigned to different groups by formal randomization? How were the 3 pups per litter chosen? (Michael S. Lauer).

I believe detailed information about animal selection and randomization procedures should be given so that the potential for allocation bias could be judged. (Aleksandra M. Michalowski)

Pregnant dams were assigned to groups, including the control group, using formal randomization that sought to also equalize mean body weights across groups. The three pups per sex per litter were selected using formal randomization, as well. Tumors in the heart and brain were not observed in littermates, indicating that there was no litter-based bias in the results.

Were all analyses based on the intent-to-treat principle? Were there any crossovers? Were all rats accounted for by the end of the experiment and were all rats who started in the experiment included in the final analyses? (Michael S. Lauer)

The intent-to-treat principle is not relevant to this animal experiment, in which all animals that were assigned to a treatment group received the full and equal treatment of that group. There were no crossovers. All animals that started the experiment were accounted for by the end of the experiment and included in the final analyses.

The PWG review blinding was not complete. (Michael S. Lauer)

PWG reviewers were blinded to the identity of the test article and the level of exposure but were not blinded to the fact that there were two different, yet related, test articles (modulations of cell phone RFR), to emphasize the fact that there was a common control group.

Did the authors perform a prospective sample size calculation? (Michael S. Lauer)

If power calculations to determine the required sample size were performed, the results should also be included. (Aleksandra M. Michalowski)

Sample size calculations were conducted for this study. However, for detecting carcinogenesis, sample size and power will depend on the baseline (control) tumor rate and the expected magnitude of the increase in tumors. For example, at 80% power, sample size requirements will be quite different for detecting a 2-fold increase in a rare tumor having a spontaneous occurrence of 0.5% compared to a 2-fold increase in a more common tumor having a spontaneous occurrence of 10%. Because many different tumor types having a wide range of spontaneous occurrence are involved in these studies, there is no “one-size-fits-all” sample size; rather, the sample size is a

compromise among several factors, including obtaining reasonable power to detect moderate to large increases for most tumor types, while staying within budgets of time, space, and funding. A sample of 90 animals per sex per group was selected as providing as much statistical power as possible across the spectrum of tumors, under the constraints imposed by the exposure system.

The NTP's carcinogenicity studies are similar in structure to the OECD's 451 Guideline for carcinogenicity studies and the FDA's guidance for rodent carcinogenicity studies of pharmaceuticals. These guidelines recommend at least 50 animals of each sex per group, but also mention that an increase in group size provides relatively little increase in statistical power. In the NTP's RFR studies, the group sizes were 90 animals of each sex per group, nearly twice as many as the minimum recommendation. Increasing the group sizes further provides diminishing returns, for which additional animals do not substantially increase power.

The low power implies that there is a high risk of false positive findings (citing Ioannidis, 2005). … I suspect that this experiment is substantially underpowered and that the few positive results found reflect false positive findings (citing Ioannidis, 2005). (Michael S. Lauer)

It is true that the power is low for detecting moderate increases above a low background tumor rate of approximately 1 – 2 %, as was seen in the brain and heart tumors. However, this low power does not correspond to a high risk of false positive findings. The paper by Ioannidis that was cited correctly states that when studies are small or effect sizes are small (i.e., statistical power is low), "the less likely the research findings are to be true." Research findings can be "not true" if the result is a false positive or a false negative. With low statistical power, false negatives are much more likely than false positives. Therefore, the vast majority of false research findings in a low power situation will result from the failure to detect an effect when it exists. The false positive rate on any properly constructed statistical test will not exceed its significance level, alpha. By definition, the significance level of a statistical test is its false positive rate, and it is typically selected by the researcher, often at a low fixed value such as 0.05 or 5%.

If we were repeating the experiment, we may see some control studies have 1 or more tumors. (Max Lee) (Dr. Lee also presented analyses of the male rat data, inserting hypothetical data on one tumor-bearing animal in the control group.)

In light of the historical control data, Dr. Lee demonstrated that several associations became less or not significant with the insertion of a tumor data point in the control group. While we appreciate that some other studies had one or more tumors, the NTP considers the concurrent control group as the most important comparator to the treated groups. We took the historical control tumor rates into account in a more subjective manner in our interpretation of the findings. In 2010, we asked to adopt a more formal method of incorporating historical control data in our statistical testing, but our Board of Scientific Counselors voted against adopting the method.

It is puzzling why the control had short survival rate. Given that most of the gliomas and heart schwannomas are late-developing tumors, it is possible that if the controls were living longer some tumors might develop. Although the use of poly-3 (or poly-6) test intended to adjust the number of rats

used in the study, it is still important to re-evaluate the analysis by considering the incidence rate in controls not being 0. (Max Lee)

We do not know why the male rat control group had a low survival rate. We generally do observe lower survival rates in studies such as the RFR studies in which animals are singly- rather than group housed. While some tumors might possibly have arisen in controls if they lived longer, it was notable that no glial cell or Schwann cell hyperplasias were found in these animals as well.

The poly-k (e.g., poly-3 or poly-6) test was developed to adjust for the fact that not all animals survive to the end of a two-year study, and survival rates may differ among groups. The test is essentially a Cochran-Armitage trend test in which the denominator of the tumor rate in each group is adjusted downward to better reflect the number of animal-years at risk during the study. Each animal that develops the tumor or survives to the end of the study is counted as one animal. Each animal that does not develop the tumor and dies (or is moribund sacrificed) before the end of the study is counted as a fractional animal. The fraction is calculated as the proportion of the study that it survived, raised to the k-th power; k = 3 or k = 6 in this study. The survival-adjusted tumor rate in each group is then the number of animals having the tumor of interest divided by the total count of animals at risk of developing the tumor in the group. These survival-adjusted rates are used in the Cochran-Armitage formula to provide the poly-k test for dose-related trends and pairwise comparisons with the control group.

The poly-k test has been shown to yield valid inferences about tumor rates in NTP two-year rat and mouse carcinogenicity studies (Bailer and Portier, 1988; Portier and Bailer, 1989; Portier et al., 1986). Its theoretical basis is that tumor incidence, while not directly observed unless the tumor is immediately lethal, follows a Weibull distribution with a shape parameter, k. Verification using NTP studies has shown that if k is between 1 and 5, setting k = 3 yields a valid statistical test (Portier and Bailer, 1989; Portier et al, 1986). Thus, most of the time, the NTP uses the poly-3 test. If a tumor type is late-occurring, as we observed with the brain gliomas, k = 6 is a better fit to the data and the poly-6 test has more validity.

In the portion of the text describing differences in survival at the end of the study between control and RFR-exposed animals the compared characteristic is not named and also no numerical values of the estimates or the range of differences are given. I would add numbers in the text of an Appendix table showing the group survival estimates described in this paragraph. (Aleksandra M. Michalowski)

The Statistical Methods section describes the method for comparing survival distributions between the control and RFR-exposed groups, namely, Tarone's (1975) life table test to identify exposure-related trends in survival and Cox's (1972) method for testing two groups for equality of survival distributions.

References

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ADDITIONAL RESPONSE:

Dear All,

Thanks again for all your helpful comments on the NTP RFR studies. I did want to follow up on one remaining point of disagreement that Mike Lauer alluded to in his comments about low powered studies. Although we agree that our study design had low power to detect statistically significant neoplastic effects in the brain and heart, which occurred with both RFR modulations in male rats, we disagree over the assertion that low power in and of itself, creates false positive results. We cited a handful of publications outlining the statistical arguments against this with specific respect to the NTP rodent cancer study design in our response to comments document sent earlier. Although Mike referred to the example of positive findings in underpowered epidemiology studies that could not be replicated in larger follow up studies, there is a growing literature alluding to this problem with respect to experimental animal studies as well. An example is a relatively recent article by one of our collaborators in CAMARADES, Malcolm MacLeod.

http://www.nature.com/news/2011/110928/full/477511a.html

It's important to distinguish between low power to detect effects, and the constellation of other factors that often accompany low powered experimental animal studies in contributing to this problem. We've addressed this issue in a recent editorial, and these factors are captured in our published systematic review process for evaluating study quality in environmental health sciences (Rooney et al., 2014).

http://ehp.niehs.nih.gov/wp-content/uploads/122/7/ehp.1408671.pdf

http://ehp.niehs.nih.gov/wp-content/uploads/122/7/ehp.1307972.pdf

Table 1 in the Rooney et al. report outlines risk of bias considerations that commonly plague studies carried out by academic researchers that are accounted for in NTP studies.

I provide these examples to assure you that we are completely cognizant of these issues and take them very seriously. Again, we appreciate the help you've provided in assuring that we appropriately interpret and communicate our findings.

Best
John Bucher

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REVIEW ARTICLE

Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation

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ABSTRACT
This review aims to cover experimental data on oxidative effects of low-intensity radiofrequency radiation (RFR) in living cells. Analysis of the currently available peer-reviewed scientific literature reveals molecular effects induced by low-intensity RFR in living cells; this includes significant activation of key pathways generating reactive oxygen species (ROS), activation of peroxidation, oxidative damage of DNA and changes in the activity of antioxidant enzymes. It indicates that among 100 currently available peer-reviewed studies dealing with oxidative effects of low-intensity RFR, in general, 93 confirmed that RFR induces oxidative effects in biological systems. A wide pathogenic potential of the induced ROS and their involvement in cell signaling pathways explains a range of biological/health effects of low-intensity RFR, which include both cancer and non-cancer pathologies. In conclusion, our analysis demonstrates that low-intensity RFR is an expressive oxidative agent for living cells with a high pathogenic potential and that the oxidative stress induced by RFR exposure should be recognized as one of the primary mechanisms of the biological activity of this kind of radiation.

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Introduction

Intensive development of wireless technologies during the last decades led to a dramatic increase of background radiofrequency radiation (RFR) in the human environment. Thus, the level of indoor background RFR in industrialized countries increased 5,000-fold from 1985 to 2005 (Maes, 2005). Such significant environmental changes may have a serious impact on human biology and health. As a proof of such impact, a series of epidemiological studies on the increased risk of tumorigenesis in "heavy" users of wireless telephony exists (Hardell et al., 2007, 2011; Sadetzki et al., 2008; Sato et al., 2011). Some studies indicate that long-term RFR exposure in humans can cause various non-cancer disorders, e.g., headache, fatigue, depression, tinnitus, skin irritation, hormonal disorders and other conditions (Abdel-Rassoul et al., 2007; Buchner & Eger, 2011; Chu et al., 2011; Johansson, 2006; Santini et al., 2002; Yakymenko et al., 2011). In addition, convincing studies on hazardous effects of RFR in human germ cells have been published (Agarwal et al., 2009; De Iuliis et al., 2009).

All abovementioned studies dealt with the effects of low-intensity RFR. This means that the intensity of radiation was far below observable thermal effects in biological tissues, and far below safety limits of the International Commissions on Non-Ionizing Radiation Protection (ICNIRP) (ICNIRP, 1998). To date, molecular mechanisms of non-thermal effects of RFR are still a bottleneck in the research on the biological/health effects of low-intensity RFR, although recently many studies have been carried out on metabolic changes in living cells under low-intensity RFR, and comprehensive reviews were published (Belyaev, 2010; Consales et al., 2012; Desai et al., 2009; Yakymenko et al., 2011). In the present work, we analyze the results of molecular effects of low-intensity RFR in living cells and model systems, with a special emphasis on oxidative effects and free radical mechanisms. It might seem paradoxical that, despite being non-ionizing, RFR can induce significant activation of free radical processes and overproduction of reactive oxygen species (ROS) in living cells. We believe that the analysis of recent findings will allow recognition of a

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general picture of the potential health effects of already ubiquitous and ever-increasing RFR.

Radiofrequency radiation

RFR is a part of electromagnetic spectrum with frequencies from 30 kHz to 300 GHz. RFR is classified as non-ionizing, which means that it does not carry sufficient energy for ionization of atoms and molecules. A part of RFR with the highest frequencies (300 MHz to 300 GHz) is referred to as microwaves (MWs). MW is RFR with the highest energy, which can potentially generate the highest thermal effects in the absorbing matter.

The main indexes of RFR are (i) frequency (Hz); (ii) intensity or power density (PD) of radiation (W/m^2 or $\mu W/cm^2$); (iii) its modulated or non-modulated nature; and (iv) continuous or discontinuous pattern of radiation. For the absorbed RFR energy, a parameter of specific absorption rate (SAR) is used (W/kg). The most common digital standard of RFR for mobile communication is still GSM (Global System for Mobile communication), which utilizes frequencies at about 850, 900, 1800 and 1900 MHz. This radiation is frequency modulated, with channel rotation frequency of 217 Hz, and belongs to the radiation of the pulsed mode (Hyland, 2000).

As to the international safety limits, the ICNIRP recommendations restrict intensity of RFR to 450–1000 $\mu W/cm^2$ (depending on the frequency of radiation) and the SAR value to 2 W/kg, as calculated for human heads and torsos (ICNIRP, 1998). These indexes were adopted by ICNIRP based on the behavioral response of laboratory rats, which were exposed to gradually increased intensities of RFR to determine the point at which the animals became thermally distressed (Gandhi et al., 2012).

Low-intensity RFR is referred to as radiation with intensities which do not induce significant thermal effects in biological tissues. Accordingly, any intensity of RFR under the ICNIRP limits can be referred to as low-intensity. In this paper we will analyze only the effects of low-intensity RFR.

Physical/biophysical effects of low-intensity RFR in living cells

RFR, especially MW, can produce thermal effects in matter due to interaction with charged particles, including free electrons, ions or polar molecules, inducing their oscillations in electromagnetic field. The thermal effect of MW can be seen when warming food in the microwave. The effect strongly depends on the intensity of radiation and is mostly negligible under low-intensity RFR conditions. On the other hand, energy of RFR/MW is insufficient not only for the ionization of molecules, but even for activation of orbital electrons. Hence, RFR was often assessed as a factor producing only thermal effects. Nevertheless, evident biological effects of low-intensity RFR promoted research on physical mechanisms of non-thermal biological effects of this kind of radiation.

A biophysical model of a forced-vibration of free ions on the surface of a cell membrane due to external oscillating electromagnetic field (EMF) was proposed (Panagopoulos et al., 2000, 2002). According to the authors, this vibration of electric charges can cause disruption of the cellular electrochemical balance and functions.

A "moving charge interaction" model was proposed for low-frequency EMF (Blank and Soo, 2001). The authors explained activation of genes and synthesis of stress proteins under EMF exposure due to interaction of the field with moving electrons in DNA (Blank and Soo, 2001; Goodman and Blank, 2002). They also demonstrated that EMF increased electron transfer rates in cytochrome oxidase and accelerated charges in the Na,K-ATPase reaction. Moreover, they demonstrated acceleration of the oscillating Belousov–Zhabotinski reaction in homogeneous solutions due to the application of low-frequency EMF (Blank and Soo, 2003).

An ability of low-strength magnetic fields to trigger onset- and offset-evoked potentials was demonstrated (Marino et al., 2009). Effectiveness of a rapid magnetic stimulus (0.2 ms) has led the authors to a conclusion on direct interaction between the field and ion channels in plasma membrane. A plausible mechanism of overproduction of free radicals in living cell due to electron spin flipping in confined free radical pairs in magnetic field of RFR was proposed (Georgiou, 2010).

A significant effect of low-intensity RFR on ferritin, an iron cage protein present in most living organisms from bacteria to humans, was revealed (Céspedes and Ueno, 2009). Exposure of ferritin solution to low-intensity RFR significantly, up to threefold, reduced iron chelation with ferrozine. The authors explained that magnetic field of RFR plays a principle role in the observed effect, and that this effect is strongly non-thermal. The non-thermal mechanism of the interaction of RFR magnetic fields with ferritin is supposedly mediated by an inner super-paramagnetic nanoparticle ($9H_2O \times 5Fe_2O_3$ with up to 4500 iron ions), which is a natural phenomenon intrinsic to the cells. It results in reduction of input of iron chelates into the ferritin cage. The authors underlined the potential role of ferritin

malfunction for oxidative processes in living cell due to the participation of Fe^{2+} ions in the Fenton reaction, which produces hydroxyl radicals. In this respect, it is interesting to point to the results of an *in vitro* study with RFR exposure of rat lymphocytes treated by iron ions (Zmyślony et al., 2004). Although RFR exposure (930 MHz) did not induce detectable intracellular ROS overproduction, the same exposure in the presence of $FeCl_2$ in the lymphocyte suspensions induced a significant overproduction of ROS.

Another set of studies indicates on a possibility of changes in protein conformation under RFR exposure. Thus, low-intensity 2.45 MHz RFR accelerated conformational changes in β-lactoglobulin through excitation of so-called collective intrinsic modes in the protein (Bohr and Bohr, 2000a, 2000b), which suggests a principal ability of RFR to modulate the non-random collective movements of entire protein domains. Similarly, a frequency-dependent effect on intrinsic flexibility in insulin structure due to applied oscillating electric field was demonstrated (Budi et al., 2007). Moreover, macromolecular structure of cytoskeleton was significantly altered in fibroblasts of Chinese hamster after the exposure to modulated RFR of the GSM standard (Pavicic and Trosic, 2010). Thus, a 3 h exposure of fibroblasts to modulated RFR (975 MHz) led to significant changes in the structure of microtubules and actin microfilaments, which have polar cytoskeleton structures, while non-polar vimentin filaments reportedly stayed unchanged. Taking into account an extensive regulatory potential of cytoskeleton on cell homeostasis, these data could obviously add to the nature of the biological effects of RFR.

It was shown that ornithine decarboxylase (ODC) can significantly change its activity under low-intensity RFR exposure (Byus et al., 1988; Hoyto et al., 2007; Litovitz et al., 1993, 1997; Paulraj et al., 1999).

In addition, so-called "calcium effects" under RFR exposure in living cells have been demonstrated (Dutta et al., 1989; Paulraj et al., 1999; Rao et al., 2008), which include a significant increase in intracellular Ca^{2+} spiking. Taking into account that calcium is a ubiquitous regulator of cellular metabolism, these data point to a possibility that non-thermal RFR can activate multiple Ca^{2+}-dependent signaling cascades.

Finally, an ability of low-intensity MW to dissociate water molecules was demonstrated in model experiments years ago (Vaks et al., 1994). In these experiments, MW of 10 GHz with radiated power 30 mW produced a significant level of H_2O_2 in deionized water (and also in $MgSO_4$ solution) under stable temperature conditions. According to the authors, a kinetic excitation of liquid water associates $C(H_2O)$ upon the absorption of MW leads to subsequent viscous losses due to friction between moving clusters of water molecules. It results in partial irreversible decomposition of water, including breaks of intramolecular bonds (H–OH) due to a mechanochemical reaction, and generation of $H^•$; $OH^•$; H^+ and $OH^−$ groups. Among these, the hydroxyl radical ($OH^•$) is the most aggressive form of ROS, which can break any chemical bond in surrounding molecules (Halliwell, 2007). The authors assessed that this type of mechanochemical transformation in water could be responsible for $10^{−4}$–$10^{−8}$ relative parts of the total MW energy absorbed. Given the fact that the water molecules are ubiquitous in living cells, even a subtle chance for dissociation of water molecules under low-intensity RFR exposure could have a profound effect on tissue homeostasis. It is of note here that one $OH^•$ radical can initiate irreversible peroxidation of many hundreds of macromolecules, e.g. lipid molecules (Halliwell, 1991). Taken together, these data show that non-thermal RFR can be absorbed by particular charges, molecules and cellular structures, and in this way can potentially induce substantial modulatory effects in living cell.

Generation of reactive oxygen species under RFR exposure in living cells

NADH oxidase of cellular membrane was suggested as a primary mediator of RFR interaction with living cells (Friedman et al., 2007). Using purified membranes from HeLa cells, the authors experimentally proved that the exposure to RFR of 875 MHz, 200 μW/cm^2 for 5 or 10 min significantly, almost threefold, increased the activity of NADH oxidase. NADH oxidases are membrane-associated enzymes that catalyze one-electron reduction of oxygen into superoxide radical using NADH as a donor of electron, thus producing powerful ROS. This enzyme has been traditionally known due to its role in induction of oxidative burst in phagocytes as a part of immune response. Yet, later the existence of non-phagocytic NAD(P)H oxidases was revealed in various types of cells, including fibroblasts, vascular and cardiac cells (Griendling et al., 2000). Obviously, the presence of superoxide-generating enzyme in many types of non-phagocytic cells points to the considerable regulatory roles of ROS in living cells. On the other hand, an ability of low-intensity RFR to modulate the activity of the NADH oxidase automatically makes this factor a notable and potentially dangerous effector of cell metabolism. Notably, the authors pointed out that the acceptor of RFR is different from the peroxide-generating NADPH oxidases, which are also found in plasma membranes (Low et al., 2012).

The other powerful source of ROS in cells is mitochondrial electron transport chain (ETC), which can generate superoxide due to breakdowns in electron transport (Inoue et al., 2003). It was demonstrated that generation of ROS by mitochondrial pathway can be activated under RFR exposure in human spermatozoa (De Iuliis et al., 2009). The authors revealed a dose-dependent effect of 1.8 GHz RFR exposure on ROS production in spermatozoa, particularly in their mitochondria. The significantly increased level of total ROS in spermatozoa was detected under RFR with SAR = 1 W/kg, which is below the safety limits accepted in many countries. It was demonstrated recently in our laboratory that the exposure of quail embryos *in ovo* to extremely low-intensity RFR (GSM 900 MHz, 0.25 μW/cm^2) during the initial days of embryogenesis resulted in a robust overproduction of superoxide and nitrogen oxide radicals in mitochondria of embryonic cells (Burlaka et al., 2013). It is not clear yet which particular part of ETC is responsible for the interaction with RFR. To date, three possible sites of generation of superoxide in ETC have been shown: the ETC complex I (Inoue et al., 2003), complex II (Liu et al., 2002), and complex III (Guzy and Schumacker, 2006). A significant inverse correlation between mitochondrial membrane potential and ROS levels in living cell was found (Wang et al., 2003). As the authors underlined, such a relationship could be due to two mutually interconnected phenomena: ROS causing damage to the mitochondrial membrane, and the damaged mitochondrial membrane causing increased ROS production.

In addition to the well-established role of the mitochondria in energy metabolism, regulation of cell death is a second major function of these organelles. This, in turn, is linked to their role as the powerful intracellular source of ROS. Mitochondria-generated ROS play an important role in the release of cytochrome c and other pro-apoptotic proteins, which can trigger caspase activation and apoptosis (Ott et al., 2007). A few reports indicate on activation of apoptosis due to low-intensity RFR exposure. In human epidermoid cancer KB cells, 1950 MHz RFR induced time-dependent apoptosis (45% after 3 h) that is paralleled by 2.5-fold decrease of the expression of ras and Raf-1 and of the activity of ras and Erk-1/2 (Caraglia et al., 2005). Primary cultured neurons and astrocytes exposed to GSM 1900 MHz RFR for 2 h demonstrated up-regulation of caspase-2, caspase-6 and Asc (apoptosis associated speck-like protein containing a card) (Zhao et al., 2007). Up-regulation in neurons occurred in both "on" and "stand-by" modes, but in astrocytes only in the "on" mode. We should underline that, in that study an extremely high biological sensitivity to RFR was demonstrated, as a cell phone in the "stand-by" position emits negligibly low-intensity of radiation (up to hundredths μW/cm^2).

Based on the analysis of available literature data, we identified altogether 100 experimental studies in biological models which investigated oxidative stress due to low-intensity RFR exposures. From these 100 articles, 93 studies (93%) demonstrated significant oxidative effects induced by low-intensity RFR exposure (Table 1–3), while 7 studies (7%) demonstrated the absence of significant changes (Table 4). The total number includes 18 *in vitro* studies, 73 studies in animals, 3 studies in plants and 6 studies in humans. Majority of the research was done on laboratory rats (58 studies, with 54 positive results), while 4 studies out of 6 in humans were positive. From the *in vitro* studies, 17 were positive (94.4%), including 2 studies on human spermatozoa and 2 studies on human blood cells.

Most of the studies utilized RFR exposure in MW range, including a use of commercial or trial cell phones as sources of radiation. The power densities of RFR applied in positive studies varied from 0.1 μW/cm^2 (Oksay et al., 2014) to 680 μW/cm^2 (Jelodar et al., 2013) and SAR values varied from 3 μW/kg (Burlaka et al., 2013) to the ICNIRP recommended limit of 2 W/kg (Naziroglu et al., 2012a; Xu et al., 2010). Exposure times in positive studies varied from 5 min (Friedman et al., 2007) to 12.5 years, 29.6 h/month (Hamzany et al., 2013).

The most often used indexes of oxidative stress analyzed in the studies were ROS production, levels of lipid peroxidation (LPO)/malondialdehyde (MDA), protein oxidation (PO), nitric oxides (NO_x), glutathione (GSH), activity of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px)). It is important that some studies directly pointed to induction of free radicals (superoxide radical, NO) as a primary reaction of living cells to RFR exposure (Burlaka et al., 2013; Friedman et al., 2007). As we pointed out earlier, direct activation of NADH oxidase (Friedman et al., 2007) and the mitochondrial pathway of superoxide overproduction (Burlaka et al., 2013; De Iuliis et al., 2009) have been experimentally proven. Besides, a significant overproduction of nitrogen oxide was revealed in some studies (Avci et al., 2012; Bilgici et al., 2013; Burlaka et al., 2013), although it is unclear whether an induction of expression of NO-synthases or direct activation of the enzyme took place. It is however clear that significantly increased levels of these free radical species (superoxide and nitrogen oxide) in cells due to RFR exposure result in an activation of peroxidation and repression of activities of key antioxidant enzymes. It is indicative that many studies demonstrated effectiveness of different

Table 1. Publications which reported positive findings on oxidative stress caused by RFR exposure of cells *in vitro*.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Agarwal et al., 2009)	Human spermatozoa	Cell phone RFR, in talk mode, for 1 h	Increase in reactive oxygen species (ROS) level, decrease in sperm motility and viability.
(Campisi et al., 2010)	Rat astroglial cells	900 MHz (continuous or modulated), electric field 10 V/m, for5; 10; 20 min	Increase in ROS levels and DNA fragmentation after exposure to modulated RFR for 20 min.
(De Iuliis et al., 2009)	Human spermatozoa	1.8 GHz, SAR = 0.4–27.5 W/kg	Increased amounts of ROS.
(Friedman et al., 2007)	HeLa membranes	875 MHz, 200 μW/cm^2, for 5 and 10 min	Increased NADH oxidase activity.
(Hou et al., 2014)	Mouse embryonic fibroblasts (NIH/3T3)	1800-MHz GSM-talk mode RFR, SAR = 2 W/kg, intermittent exposure (5 min on/ 10 min off) for 0.5–8 h	Increased intracellular ROS levels.
(Kahya et al., 2014)	Cancer cell cultures	900 MHz RFR, SAR = 0.36 W/kg, for 1 h	Induced apoptosis effects through oxidative stress, selenium counteracted the effects of RFR exposure.
(Lantow et al., 2006a)	Human blood cells	Continuous wave or GSM signal,SAR = 2 W/kg, for 30 or 45 min of continuous or 5 min ON, 5 min OFF	After continuous or intermittent GSMsignal a different ROS production was detected in human monocytes compared to sham.
(Lantow et al., 2006b)	Human Mono Mac 6 and K562 cells	Continuous wave, GSM speaking only, GSM hearing only, GSM talk, SARs of 0.5, 1.0, 1.5 and 2.0 W/kg.	The GSM-DTX signal at 2 W/kg produced difference in free radical production compared to sham.
(Liu et al., 2013b)	GC-2 cells	1800 MHz, SAR = 1; 2 W/kg,5 min ON, 10 min OFF for 24 h	In the 2 W/kg exposed cultures, the level of ROS was increased.
(Lu et al., 2012)	Human blood mononuclear cells	900 MHz, SAR = 0.4 W/kg, for 1–8 h	The increased level of apoptosis induced through the mitochondrial pathway and mediated by activating ROS and caspase-3.
(Marjanovic et al., 2014)	V79 cells	1800 MHz, SAR = 1.6 W/kg, for 10, 30 and 60 min	ROS level increased after 10 min of exposure. Decrease in ROS level after 30-min treatment indicating antioxidant defense mechanism activation.
(Naziroglu et al., 2012b)	HL-60 cells	2450 MHz, pulsed, SAR = 0.1–2.5 W/kg, for 1; 2; 12 or 24 h	Lipid peroxide (LPO) levels were increased at all exposure times.
(Ni et al., 2013)	Human lens epithelial cells	1800 MHz, SAR = 2; 3; 4 W/kg	The ROS and malondialdehyde (MDA) levels were increased.
(Pilla, 2012)	Neuronal cells and human fibroblasts	27.12 MHz, pulsed, electric field 41 V/m, 2 min prior to lipopolysaccharide administration or for 15 min	Increased level of nitric oxide (NO).
(Sefidbakht et al., 2014)	HEK293T cells	940 MHz, SAR = 0.09 W/kg, for 15, 30, 45, 60 and 90 min	ROS generation increased in the 30 min exposed cells. A sharp rise in catalase (CAT) and superoxide dismutase (SOD) activity and elevation of glutathione (GSH) during the 45 min exposure.
(Xu et al., 2010)	Primary cultured neurons	1800 MHz, pulsed, SAR = 2 W/kg, for 24 h	An increase in the levels of8-hydroxy-2'-deoxyguanosine (8-OH-dG).
(Zmyślony et al., 2004)	Rat lymphocytes	930 MHz, PD of 500 μW/cm^2, SAR = 1.5 W/kg, for 5 and 15 min	Intracellular ROS level increased in exposed $FeCl_2$ treated cells compared with unexposed $FeCl_2$ treated cells.

*All effects were statistically significant (at least $p < 0.05$) as compared to control or sham exposed groups.

antioxidants to override oxidative stress caused by RFR exposure. Such effects have been reported for melatonin (Ayata et al., 2004; Lai and Singh, 1997; Oktem et al., 2005; Ozguner et al., 2006; Sokolovic et al., 2008), vitamin E and C (Jelodar et al., 2013; Oral et al., 2006), caffeic acid phenethyl ester (Ozguner et al., 2006), selenium, L-carnitine (Turker et al., 2011) and garlic (Avci et al., 2012; Bilgici et al., 2013).

It is worthwhile to emphasize a strict non-thermal character of ROS overproduction under RFR exposure described in the cited reports. As low as 0.1 μW/cm^2 intensity of RFR and absorbed energy (specific absorption rate, SAR) of 0.3 μW/kg were demonstrated to be effective in inducing significant oxidative stress in living cells (Burlaka et al., 2013; Oksay et al., 2014). This observation is particularly important as the modern international safety limits on RFR exposure are based solely on the thermal effects of radiation and only restrict RFR intensity to 450–1000 μW/cm^2 and SAR to 2 W/kg (ICNIRP, 1998). Moreover, studies where high (thermal) intensities of RFR have been used could not reveal oxidative effects (Hong et al., 2012; Kang et al., 2013; Luukkonen et al., 2009), which might point to the variety of molecular mechanisms for different radiation intensities.

Taken together, the analysis of the contemporary scientific literature on the biological effects of RFR persuasively proves that the exposure to low-intensity RFR in living cells leads to generation of significant levels of ROS and results in a significant oxidative stress.

Oxidative damage of DNA under RFR exposure

To date more than hundred papers have been published on mutagenic effects of RFR and most of them revealed significant effects (Ruediger, 2009). There is a substantial number of studies which demonstrated the formation of micronuclei (Garaj-Vrhovac et al., 1992; Tice et al., 2002; Zotti-Martelli et al., 2005) or structural anomalies of metaphase chromosomes (Garson et al., 1991; Kerbacher et al., 1990; Maes et al., 2000) in living

Table 2. Publications which reported positive findings on oxidative stress caused by RFR exposure of animals and plants.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Akbari et al., 2014)	Rat whole body	RFR from base transceiver station	Glutathione peroxidase (GSH-Px), SOD, and CAT activity decreased and level of MDA increased. Vitamin C reduced the effect.
(Al-Damegh, 2012)	Rat whole body	Cell phone RFR, 15, 30, or 60 min/day for 2 weeks	Levels of conjugated dienes, LPO and CAT activities in serum and testicular tissue increased, the total serum and testicular tissue GSH and GSH-Px levels decreased.
(Avci et al., 2012)	Rat whole body	1800 MHz, SAR = 0.4 W/kg, 1 h/day for 3 weeks	An increased level of protein oxidation (PO) in brain tissue and an increase in serum NO. Garlic administration reduced protein oxidation in brain tissue.
(Ayata et al., 2004)	Rat whole body	900 MHz, 30 min/day for 10 days	MDA and hydroxyproline levels and activities of CAT and GSH-Px were increased, andsuperoxide dismutase (SOD) activity was decreased in skin. Melatonin treatment reversed effect.
(Aynali et al., 2013)	Rat whole body	2450 MHz, pulsed, SAR = 0.143 W/kg,60 min/day for 30 days	LPO was increased, an administration of melatonin prevented this effect.
(Balci et al., 2007)	Rat whole body	"Standardized daily dose" of cell phoneRFR for 4 weeks	In corneal tissue, MDA level and CAT activity increased, whereas SOD activity was decreased. In the lens tissues, the MDA level was increased.
(Bilgici et al., 2013)	Rat whole body	850–950 MHz,SAR = 1.08 W/kg,1 h/day for 3 weeks	The serum NO levels and levels of MDA and the PO in brain were increased. An administration of garlic extract diminished these effects.
(Bodera et al., 2013)	Rat whole body	1800 MHz, GSM, for 15 min	Reduced antioxidant capacity both in healthy animals and in those with paw inflammation.
(Burlaka et al., 2013)	Quail embryo *in ovo*	GSM 900 MHz, power density (PD) of 0.25 μW/cm^2, SAR = 3 μW/kg, 48 sec ON - 12 sec OFF, for 158–360 h	Overproduction of superoxide and NO, increased levels of thiobarbituric acid reactive substances (TBARS) and 8-OH-dG, decreased SOD and CAT activities.
(Burlaka et al., 2014)	Male rat whole body	Pulsed and continuous MWin the doses equivalent to the maximal permitted energy load for the staffs of the radar stations	Increased rates of superoxide production, formation of the iron-nitrosyl complexes and decreased activity of NADH-ubiquinone oxidoreductase complex in liver, cardiac and aorta tissues 28 days after the exposure.
(Cenesiz et al., 2011)	Guinea pig whole body	900; 1800 MHz RFR from base station antennas, 4 h/day for 20 days	Difference in guinea pigs subjected to 900 and 1800 MHz for plasma oxidant status levels. NO level changed in 900 MHz subjected guinea pigs, as compared to the control.
(Cetin et al., 2014)	Pregnant rats and offspring	900; 1800 MHz RFR, 1 h/day during pregnancy and neonatal development	Brain and liver GSH-Px activities, selenium concentrations in the brain and liver vitamin A and β-carotene concentrations decreased in offspring.
(Dasdag et al., 2009)	Head of rats	900 MHz, 2 h/day for 10 months	The total antioxidant capacity and CATactivity in brains were higher than that in the sham group.
(Dasdag et al., 2012)	Head of rats	900 MHz, cell-phones-like, 2 h/day for 10 months	Protein carbonyl level was higher in the brain of exposedrats.
(Dasdag et al., 2008)	Rat whole body	900 MHz, PD of 78 μW/cm^2, 2 h/days for10 months.	Increased levels of MDA and total oxidative status in liver tissue.
(Deshmukh et al., 2013)	Rat whole body	900 MHz, 2 h/day, 5 days a week for 30 days	The levels of LPO and PO were increased.
(Esmekaya et al., 2011)	Rat whole body	900 MHz, pulsed, modulated, SAR = 1.2 W/kg, 20 min/day for 3 weeks	The increased level of MDA and NOx, and decreased levels of GSH in liver, lung, testis and heart tissues.
(Furtado-Filho et al., 2014)	Rat whole body	950 MHz, SAR = 0.01–0.88 W/kg,30 min/day for 21 days during pregnancy (or additionally 6 or 15 days of postnatal period)	Neonatal rats exposed in utero had decreased levels of CAT and lower LPO, and genotoxic effect.
(Guler et al., 2012)	Rabbit infant whole body	GSM 1800 MHz, 15 min/day for 7 days (females) or 14 days (males)	LPO levels in the liver tissues of females and males increased,liver 8-OH-dG levels of females were increased.
(Guney et al., 2007)	Rat whole body	900 MHz, 30 min/day for 30 days	Endometrial levels of NO and MDA increased, endometrial SOD, CAT and GSH-Px activities were decreased.Vitamin E and C treatment prevented these effects.
(Gürler et al., 2014)	Rat whole body	2450 MHz, 3.68 V/m, 1 h/day for 30 days	Increased 8-OH-dG level in both plasma and brain tissue whereas it increased PO level only in plasma. Garlic prevented the increase of 8-OH-dG level in brain tissue and plasma PO levels.
(Ilhan et al., 2004)	Rat whole body	900 MHz, from cell phone,1 h/day for 7 days	Increase in MDA, NO levels, andxanthine oxidase (XO) activity, decrease in SOD and GSH-Px activities in brain. These effects were prevented by Ginkgo bilobaextract treatment.
(Jelodar, et al., 2013)	Rat whole body	900 MHz, PD of 680 μW/cm^2, 4 h/day for 45 days,	The concentration of MDA was increased and activities of SOD, GSH-Px and CAT were decreased in rat eyes. An administration of vitamin C prevented these effects.
(Jelodar et al., 2013)	Rat whole body	900 MHz, daily for 45 days	Increased level of MDA and decreased antioxidant enzymes activity in rat testis.
(Jing et al., 2012)	Rat whole body	Cell phone RFR, SAR = 0.9 W/kg,3 x 10; 30 or 60 min for 20 days during gestation	After 30 and 60 min the level of MDA was increased, the activities of SOD and GSH-Pxwere decreased.

(*Continued*)

Table 2. (Continued).

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Kerman & Senol, 2012)	Rat whole body	900 MHz, 30 min/day for 10 days	Tissue MDA levels were increased, SOD, CAT and GSH-Pxactivities were reduced. Melatonin treatment reversed these effects.
(Kesari et al., 2010)	Male rat whole body	Cell phone RFR, SAR = 0.9 W/kg,2 h/day for 35 days	Reduction in protein kinase activity, decrease in sperm count and increase in apoptosis.
(Kesari et al., 2011)	Rat whole body	900 MHz, pulsed, SAR = 0.9 W/kg,2 h/day for 45 days	Increase in the level of ROS, decrease in the activities of SOD and GSH-Px,and in the level of pineal melatonin.
(Kesari et al., 2013)	Rat whole body	2115 MHz, SAR = 0.26 W/kg,2 h/day for 60 days	The level of ROS, DNA damage and theapoptosis rate were increased.
(Khalil et al., 2012)	Rat whole body	1800 MHz, electric field 15–20 V/m, for2 h	Elevations in the levels of 8-OH-dG in urine.
(Kismali et al., 2012)	Rabbit whole body (non-pregnant and pregnant)	1800 MHz, GSM modulation, 15 min/day for 7 days	Creatine kinases levels' changes.
(Koc et al., 2013)	Male rat whole body	Cell phone RFR at calling or stand-by	Oxidative stress detected at both calling and stand-by exposures.
(Koylu et al., 2006)	Rat whole body	900 MHz	The levels of LPO in the brain cortex and hippocampus increased.These levels in the hippocampus were decreased by melatonin administration.
(Koyu et al., 2009)	Rat whole body	900 MHz	The activities of XO, CAT and level of LPO increased in liver.XO, CAT activities and LPO levels were decreased by caffeic acid phenethyl ester (CAPE) administration.
(Kumar et al., 2014)	Rat whole body	Cell phone 1910.5 MHz RFR, 2 h/day for 60 days day (6 days a week).	Increase in LPO, damage in sperm cells and DNA damage.
(Lai & Singh, 1997)	Rat whole body	2450 MHz, pulsed, PD = 2 mW/cm^2, SAR = 1.2 W/kg	Melatonin or spin-trap compound blocked DNA strand breaks induced by RFR exposure in rat brain cells.
(Luo et al., 2014)	Rat whole body	900 MHz imitated cell phone RFR, 4 h/day for 12 days	Contents of liver MDA and Nrf2 protein increased, contents of liver SOD and GSH decreased.
(Mailankot et al., 2009)	Rat whole body	900/1800 MHz,GSM,1 h/day for 28 days	Increase in LPO and decreased GSH content in the testis and epididymis.
(Manta et al., 2013)	Drosophila whole body	1880–1900 MHz, DECT modulation, SAR = 0.009 W/kg, for 0.5–96 h	Increase in ROS levels in male and female bodies, a quick response in ROS increase in ovaries.
(Marzook et al., 2014)	Rat whole body	900 MHz from cellular tower, 24 h/day for 8 weeks	SOD and CAT activities were reduced in blood, sesame oil reversed the effect
(Meena et al., 2013)	Rat whole body	2450 MHz, PDof 210 μW/cm^2, SAR = 0.14 W/kg, 2 h/day for 45 days	Increased level of MDA and ROS in testis. Melatonin prevented oxidative stress.
(Megha et al., 2012)	Rat whole body	900; 1800 MHz, PD of 170 μW/cm^2, SAR = 0.6 mW/kg, 2 h/day, 5 days/week for 30 days	The levels of the LPO and PO were increased; the level of GSH was decreased.
(Meral et al., 2007)	Guinea pig whole body	890–915 MHz,from cell phone, SAR = 0.95 w/kg, 12 h/day for 30 days (11 h 45 min stand-by and 15 min spiking mode)	MDA level increased, GSH level and CAT activity weredecreased in the brain. MDA, vitamins A, D_3 and E levels and CAT enzyme activity increased, and GSH level was decreased in the blood.
(Motawi et al., 2014)	Rat whole body	Test cellphone RFR, SAR = 1.13 W/kg, 2 h/day for 60 days	Increments in conjugated dienes, protein carbonyls, total oxidant status and oxidative stress index along with a reduction of total antioxidant capacity levels.
(Naziroglu & Gumral, 2009)	Rat whole body	2450 MHz,60 min/day for 28 days	Decrease of the cortex brain vitamin A, vitamin C and vitamin E levels.
(Naziroglu et al., 2012a)	Rat whole body	2450 MHz, 60 min/day for 30 days	LPO, cell viability and cytosolic Ca^{2+} values in dorsal root ganglion neurons were increased.
(Oksay et al., 2014)	Rat whole body	2450 MHz, pulsed, PD of0.1 μW/cm^2, SAR = 0.1 W/kg, 1 h/day for 30 days	LPO was higher in exposed animals. Melatonin treatment reversed the effect.
(Oktem et al., 2005)	Rat whole body	900 MHz, 30 min/day for 10 days	Renal tissue MDA level increased, SOD, CAT and GSH-Px activities were reduced. Melatonin treatment reversed these effects.
(Oral et al., 2006)	Rat whole body	900 MHz, 30 min/day for 30 days	Increased MDA levels and apoptosis in endometrial tissue.Treatment with vitamins E and C diminished these changes.
(Ozguner et al., 2005a)	Rat whole body	900 MHz, 30 min/day for 10 days	Heart tissue MDA and NO levels increased, SOD, CAT and GSH-Px activities were reduced. CAPE treatment reversed these effects.
(Ozguner et al., 2006)	Rat whole body	900 MHz, from cell phone	Retinal levels of NO and MDA increased, SOD, GSH-Px and CAT activities were decreased.Melatonin and CAPE treatment prevented effects.
(Ozguner et al., 2005b)	Rat whole body	900 MHz	Renal tissue MDA and NO levels increased, the activities of SOD, CAT and GSH-Px were reduced. CAPE treatment reversed these effects.
(Ozgur et al., 2010)	Guinea pig whole body	1800 MHz,GSM, SAR = 0.38 W/kg, 10 or 20 min/day for 7 days	Increases in MDA and total NO(x) levels and decreases in activities of SOD, myeloperoxidase and GSH-Px in liver. Extent of oxidative damage was proportional to the duration of exposure.
(Ozgur et al., 2013)	Rabbit whole body	1800 MHz, pulsed, 15 min/day for 7 days in pregnant animals, for 7 or 15 days in infants	The amount of LPO was increased in the prenatal exposure group.

(*Continued*)

Table 2. (Continued).

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Özorak et al., 2013)	Rat whole body	900; 1800; 2450 MHz, pulsed, PD of 12 μW/cm^2. SAR = 0.18; 1.2 W/kg, 60 min/day during gestation and 6 weeks following delivery	At the age of six weeks, an increased LPO in the kidney and testis, and decreased level of GSH and total antioxidant status.
(Qin et al., 2014)	Male mouse whole body	1800 MHz, 208 μW/cm^2, 30 or 120 min/d for 30 days	Decreased activities of CAT and GSH-Px and increasedlevel of MDA in cerebrum. Nano-selenium decreased MDA level, and increased GSH-Px and CAT activities.
(Ragy, 2014)	Rat whole body	Cell phone 900 MHz RFR, 1 h/d for 60 days	Increase in MDA levels and decrease total antioxidant capacity levels in brain, liver and kidneys tissues. These alterations were corrected by withdrawal of RFR exposure during 30 days.
(Saikhedkar et al., 2014)	Rat whole body	Cell phone 900 MHz RFR, 4 h/d for 15 days	A significant change in level of antioxidant enzymes and non-enzymatic antioxidants, and an increase in LPO.
(Shahin et al., 2013)	Mouse whole body	2450 MHz, PD of 33.5 μW/cm^2, SAR = 23 mW/kg, 2 h/day for 45 days	An increase in ROS, decrease in NO and antioxidant enzymes activities.
(Sharma et al., 2009)	Plant(mung bean) whole body	900 MHz, from cell phone, PD of 8.55 μW/cm^2; for 0.5; 1; 2, and 4 h	Increased level of MDA,H_2O_2 accumulation and root oxidizability, upregulation in the activities of SOD, CAT, ascorbate peroxidases, guaiacol peroxidases and GSHreductases in roots.
(Singh et al., 2012)	Plant (mung bean) whole body	900 MHz,from cell phone	The increased level of MDA, hydrogen peroxide and proline content in hypocotyls.
(Sokolovic et al., 2008)	Rat whole body	RFR from cell phone, SAR = 0.043–0.135 W/kg, for 20, 40 and 60 days	An increase in the brain tissue MDA and carbonyl group concentration. Decreased activity of CAT and increased activity of xanthine oxidase (XO). Melatonin treatment prevented the effects.
(Sokolovic et al., 2013)	Rat whole body	900 MHz, SAR = 0,043–0.135 W/kg,4 h/day for 29; 40 or 60 days,	The level of LPO and PO, activities of CAT, XO, number of apoptotic cells were increased in thymus tissue. An administration of melatonin prevented these effects.
(Suleyman et al., 2004)	Rat whole body	Cell phoneRFR,SAR = 0.52 W/kg,20 min/day for 1 month	MDA concentration was increased in brains.
(Tkalec et al., 2007)	Plant Lemna minor (duckweed)	400 and 900 MHz, 10, 23, 41 and 120 V/m, for 2 or 4 h	LPO and H_2O_2 content increased: CAT activity increased, pyrogallol peroxidase decreased.
(Tkalec et al., 2013)	Earthworm whole body	900 MHz, PD of 30–3800 μW/cm^2, SAR = 0.13–9.33 mW/kg, for 2 h	The protein carbonyl content was increased in all exposures above 30 μWc/m^2. The level of MDA was increased at 140μW/cm^2.
(Tök et al., 2014)	Rat whole body	2450 MHz, Wi-Fi RFR, 60 min/day for 30 days	Decreased GSH-Px activity. GSH-Px activity and GSH values increased after melatonin treatment.
(Tomruk et al., 2010)	Rabbit whole body	1800 MHz, GSM-like signal, 15 min/day for a week	Increase of MDA and ferrous oxidation in xylenol orange levels.
(Tsybulin et al., 2012)	Quail embryo *in ovo*	900 MHz, fromcell phone, GSM, PD of 0.024–0.21 μW/cm^2, intermittent for 14 days	Increased level of TBARS in brains and livers of hatchlings.
(Turker et al., 2011)	Rat partial body	2450 MHz, pulsed, SAR = 0.1 W/kg,1 h/day for 28 days	The increased level of LPO, the decreased concentrations of vitamin A, vitamin C and vitamin E. There was a protective effect of selenium and L-carnitine.
(Türedi et al., 2014)	Pregnant rat whole body	900 MHz, 13.7 V/m, 50 μW/cm^2, 1 h/day for 13–21 days of pregnancy	MDA, SOD and CAT values increased, GSH values decreased in exposed pups.
(Yurekli et al., 2006)	Rat whole body	945 MHz, GSM, PD of 367 μW/cm^2, SAR = 11.3 mW/kg	MDA level and SOD activity increased, GSH concentration was decreased.

*All effects were statistically significant (at least $p < 0.05$) as compared to control or sham exposed groups.

Table 3. Publications which reported positive findings on oxidative stress caused by RFR exposure of humans.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Abu Khadra et al., 2014)	Human male head	GSM 1800 MHz from cell phone, SAR = 1.09 W/kg, for 15 and 30 min	SOD activity in saliva increased.
(Garaj-Vrhovac et al., 2011)	Human whole body	3; 5.5; 9.4 GHz, pulsed, from radars	Increased level of MDA, decreased level of GSH.
(Hamzany et al., 2013)	Human head/ whole body	RFR from cell phone a mean time of 29.6 h/ month for 12.5 years	Increase in all salivary oxidative stress indices.
(Moustafa et al., 2001)	Human male body	Cell phone in a pocket in standby position, for 1; 2 or 4 h	Plasma level of LPO was increased, activities of SOD and GSH-Px in erythrocytes decreased.

*All effects were statistically significant (at least $p < 0.05$) as compared to control or sham-exposed groups.

cells due to low-intensity RFR exposure. However, majority of the studies on the mutagenic effects of RFR successfully used a comet assay approach (Baohong et al., 2005; Belyaev et al., 2006; Diem et al., 2005; Kim et al., 2008; Lai and Singh, 1996; Liu et al., 2013a). Particular studies identified specific marker of oxidative damage of DNA, 8-hydroxy-2'-deoxyguanosine (8-OH-dG) (Burlaka et al., 2013; De Iuliis et al.,

Table 4. Publications which reported no significant oxidative effects after RFR exposure.

Reference	Biological system exposed	RFR exposure	Effects reported
(Hook et al., 2004)	Mammalian cells *in vitro*	835.62 MHz (frequency-modulated continuous-wave, FMCW) and 847.74 MHz (code division multiple access, CDMA), SAR = 0.8 W/kg, for 20–22 h	FMCW- and CDMA-modulated RFR did not alter parameters indicative of oxidative stress.
(Ferreira et al., 2006a)	Rat whole body	800–1800 MHz, from cell phone	No changes in lipid and protein damage, and in non-enzymatic antioxidant defense in frontal cortex or hippocampus.
(Ferreira et al., 2006b)	Pregnant rat whole body	RFR from cell phone	No differences in oxidative parameter of offspring blood and liver, but increase in erythrocytes micronuclei incidence in offspring.
(Dasdag et al., 2003)	Rat whole body	Cell phone RFR, SAR = 0.52 W/kg, 20 min/day for 1 month	No alteration in MDA concentration.
(Demirel et al., 2012)	Rat whole body	3G cell phone RFR, "standardized daily dose" for 20 days	No difference in GSH-Px and CAT activity in eye tissues, in MDA and GSH levels in blood.
(Khalil et al., 2014)	Human head/whole body	Cell phone RFR (talking mode) for 15 or 30 min	No relationship between exposure and changes in the salivary oxidant/antioxidant profile.
(de Souza et al., 2014)	Human head/whole body	Cell phone RFR	No difference in the saliva from the parotid gland exposed to cell phone RFR to the saliva from the opposite gland of each individual.

2009; Guler et al., 2012; Khalil et al., 2012; Xu et al., 2010). Thus, the level of 8-OH-dG in human spermatozoa was shown to be significantly increased after *in vitro* exposure to low-intensity RFR (De Iuliis et al., 2009). Likewise, we demonstrated that the exposure of quail embryos *in ovo* to GSM 900 MHz of 0.25 $\mu W/cm^2$ during a few days was sufficient for a significant, two-threefold, increase of 8-OH-dG level in embryonic cells (Burlaka et al., 2013).

It would be logical to assume that most mutagenic effects due to the RFR exposure are caused by oxidative damage to DNA, as the overproduction of ROS in living cells due to RFR exposure was reliably documented. It is known that superoxide itself does not affect DNA. The most aggressive form of ROS, which is able to affect the DNA molecule directly, is hydroxyl radical (Halliwell, 2007). The hydroxyl radicals are generated in cell in the Fenton reaction ($Fe^{2+} + H_2O_2$ -> $Fe^{3+} + OH^{\bullet} + OH^-$) and in the Haber–Weiss reaction ($O_2^{\bullet -} + H_2O_2$ -> $O_2 + OH^{\bullet} + OH^-$) (Valko et al., 2006). On the other hand, increased concentration of NO in addition to superoxide in the RFR-exposed cells can lead to the formation of other aggressive form of ROS, peroxynitrite ($ONOO^-$), which can also cause DNA damage (Valko et al., 2006).

Free radicals induced under the RFR exposure can perturb cellular signaling

Taking into account the abovementioned data, we can state that the exposure to RFR leads to overproduction of free radicals/ROS in living cell. Certainly, free radicals can induce harmful effects via direct damage due to oxidation of biological macromolecules. To that, it becomes clear nowadays that free radicals/ROS are an intrinsic part of the cellular signaling cascades (Forman et al., 2014). Thus, hydrogen peroxide appears as a second messenger both in insulin signaling and in growth factor-induced signalling cascades (Sies, 2014). These species are also implicated in biochemical mechanism of oxidation of ethanol and in other metabolic processes (Oshino et al., 1975) and is also required for initiation of wound repair (Enyedi and Niethammer, 2013). In addition, ROS at relatively low concentrations can modulate inflammation via activation of NF-kB pathway (Hayden and Ghosh, 2011). Therefore, even subtle exposures to RFR with generation of hardly detectable quantities of free radicals can have their meaningful biological consequences.

We could ascertain the signaling effects of moderate levels of free radicals from our experiments in quail embryos irradiated with the commercial cell phone. Thus, we were able to show that the prolonged exposures of embryos *in ovo* led to robust repression of their development (Tsybulin et al., 2013), which was concomitant with significant overproduction of superoxide radical and NO radical, increased rates of lipid peroxidation and oxidative damage of DNA (Burlaka et al., 2013; Tsybulin et al., 2012). Notably, shorter exposures instead led to enhancement in embryonic development (Tsybulin et al., 2012, 2013). We demonstrated the favorable effects of shorter exposures also on the molecular level. Thus, after the short-time RFR exposure the DNA comets in embryonic cells were significantly shorter than in the control non-irradiated embryos, pointing to activation of mechanisms maintaining the integrity of DNA. The "beneficial" consequences of the irradiation could be explained by hormesis effect (Calabrese, 2008). However, one could hypothesize that the "beneficial" effects of the irradiation could be explained by the signaling action of free radicals induced at levels below the damaging concentrations.

Obviously, any seemingly beneficial effect of external environmental impact should be treated with caution and possibly minimized before careful evaluation of the long-term consequences. Altogether, this gives a clear warning of the adverse health effects of low-intensity RFR, which could be evoked both by the direct oxidative damage and by disturbed cellular signaling.

Oxidative effects and non-cancer health effects of RFR

A new medical condition, so-called electrohypersensitivity (EHS), in which people suffer due to RFR exposure, has been described (Johansson, 2006). Typically, these persons suffer from skin- and mucosa-related symptoms (itching, smarting, pain, heat sensation), or heart and nervous system disorders after exposure to computer monitors, cell phones and other electromagnetic devices. This disorder is growing continuously: starting from 0.06% of the total population in 1985, this category now includes as much as 9–11% of the European population (Hallberg and Oberfeld, 2006). In Sweden, for example, EHS has become an officially recognized health impairment.

To that, a high percentage, up to 18–43% of young people, has recently been described to be suffering from headache/earache during or after cell phone conversations (Chu et al., 2011; Yakymenko et al., 2011). Likewise, a number of psychophysical and preclinical disorders including fatigue, irritation, headache, sleep disorders, hormonal imbalances were detected in high percent of people living nearby cell phone base transceiver stations (Buchner and Eger, 2011; Santini et al., 2002).

An allergy reaction to RFR in humans has been confirmed by a significant increase in the level of mast cells in skin of persons under exposure to electromagnetic devices (Johansson et al., 2001). Likewise, higher level of degranulated mast cells in dermis of EHS persons has been detected (Johansson, 2006). In turn, the activated mast cells can release histamine and other mediators of such reactions which include allergic hypersensitivity, itching, dermatoses, etc. Importantly, an implication of ROS in allergic reactions is rather clear nowadays. For example, in case of airway allergic inflammation, the lung cells generate superoxide in nanomolar concentrations following antigen challenges (Nagata, 2005). Then, mast cells generate ROS following aggregation of FcεRI, a high-affinity IgE receptor (Okayama, 2005). In addition, pollen NADPH oxidases rapidly increase the level of ROS in lung epithelium (Boldogh et al., 2005); and removal of pollen NADPH oxidases from the challenge material reduced antigen-induced allergic airway inflammation. Thus, it seems plausible that EHS-like conditions can be attributed at least partially to ROS overproduction in cells due to RFR exposures.

Oxidative effects and potential carcinogenicity of RFR

During recent years, a number of epidemiological studies indicated a significant increase in incidence of various types of tumors among long-term or “heavy” users of cellular phones (Yakymenko et al., 2011). Briefly, reports pointed to the increased risk in brain tumors (Cardis et al., 2010; Hardell and Carlberg, 2009; Hardell et al., 2007), acoustic neuroma (Hardell et al., 2005; Sato et al., 2011), tumors of parotid glands (Sadetzki et al., 2008), seminomas (Hardell et al., 2007), melanomas (Hardell et al., 2011) and lymphomas (Hardell et al., 2005) in these cohorts of people. To that, a significant increase in tumor incidence among people living nearby cellular base transceiver stations was also reported (Eger et al., 2004; Wolf and Wolf, 2007). Similarly, experimental evidences of cancer expansion in rodents caused by long-term low-intensity RFR exposure were published (Chou et al., 1992; Repacholi et al., 1997; Szmigielski et al., 1982; Toler et al., 1997). To that, activation of ODC was detected in RFR-exposed cells (Hoyto et al., 2007). ODC is involved in processes of cell growth and differentiation, and its activity is increased in tumor cells. Although overexpression of ODC is not sufficient for tumorigenic transformation, an increased activity of this enzyme was shown to promote the development of tumors from pre-tumor cells (Clifford et al., 1995).

Significant overproduction of ROS leads to oxidative stress in living cells, induces oxidative damage of DNA and can cause malignant transformation (Halliwell and Whiteman, 2004; Valko et al., 2007). It is known that in addition to mutagenic effects, ROS play a role as a second messenger for intracellular signaling cascades which can also induce oncogenic transformation (Valko et al., 2006). Earlier we hypothesized (Burlaka et al., 2013) that low-intensity RFR exposure leads to dysfunctions of mitochondria, which result in overproduction of superoxide and NO, and subsequently to ROS-mediated mutagenesis. To that, it is well established that oxidative stress is associated with carcinogenesis; for instance, the oxidative stress elicited by Membrane-Type 1 Matrix Metalloproteinase is implicated in both the pathogenesis and progression of prostate cancer (Nguyen et al., 2011). Similarly, a progressive elevation in mitochondrial ROS production (chronic ROS) under both hypoxia and/or low glucose,

which leads to stabilization of cells via increased HIF-2alpha expression, can eventually result in malignant transformation (Ralph et al., 2010). These data, together with the strong experimental evidences on activation of NADH oxidase under RFR exposure (Friedman et al., 2007) suggest that low-intensity RFR is a multifactorial stress factor for living cell, significant feature of which is oxidative effects and potential carcinogenicity as a result.

Conclusions

The analysis of modern data on biological effects of low-intensity RFR leads to a firm conclusion that this physical agent is a powerful oxidative stressor for living cell. The oxidative efficiency of RFR can be mediated via changes in activities of key ROS-generating systems, including mitochondria and non-phagocytic NADH oxidases, via direct effects on water molecules, and via induction of conformation changes in biologically important macromolecules. In turn, a broad biological potential of ROS and other free radicals, including both their mutagenic effects and their signaling regulatory potential, makes RFR a potentially hazardous factor for human health. We suggest minimizing the intensity and time of RFR exposures, and taking a precautionary approach towards wireless technologies in everyday human life.

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Declaration of interest

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STATE OF MICHIGAN

CARPENTER DEPO EXHIBIT 17

BEFORE THE MICHIGAN PUBLIC SERVICE COMMISSION

In the matter of the application and request of the DETROIT EDISON COMPANY seeking approval and authority to implement its proposed Advanced Metering Infrastructure opt out program.	)))))	Case No U-15768

QUALIFICATIONS & DIRECT TESTIMONY OF DAVID O. CARPENTER, M.D.

Q Do you swear that the testimony you are about to give is the truth, the whole truth, and nothing but the truth?

A I do.

Q Can you please state your name, address and contact information?

A. David O. Carpenter, M.D. Institute for Health and the Environment, University at Albany, Renssalear, NY 12144. Phone: 518-525-2660. email: dcarpenter@albany.edu

Q. Who are you testifying for in this proceeding?

A. Intervener David Sheldon.

Q. Are you currently in private medical practice and, if so, could you state the name of your practice and any areas of specialization within the practice?

A. I am a public health physician and as such do not hold a license to practice patient medicine. My area of specialization is environmental health and disease prevention.

Q. Are you also associated with the Institute for Health and the Environment at the University at Albany, State University of New York?

STATE OF MICHIGAN

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A. I am a public health physician and as such do not hold a license to practice patient medicine. My area of specialization is environmental health and disease prevention.

Q. Are you also associated with the Institute for Health and the Environment at the University at Albany, State University of New York?

A. Yes.

Q. Could you tell us briefly what is the scope of research done there and what is your own role at this institute?

A. I am the Director of the Institute for Health and the Environment, a Collaborating Centre of the World Health Organization. The Institute promotes interdisciplinary research on issues relation to both health and the environment in both domestic and international settings.

Q. Have you devoted a substantial part of your career to studying the effects of low-level non ionizing radiation upon human beings?

A. Yes.

Q. Do you understand the purpose of this administrative law case and why we have asked you to contribute your testimony?

A. Yes, I understand that the purpose is for evidence to be heard anew, on remand from the Michigan Court of Appeals, on whether the Commission should permit Detroit Edison Company to charge back the costs of AMI meters, aka "smart meters", to its customers. I understand the Court of Appeals has directed the Commission to consider the "risks and burdens" of AMI technology, as well as its presumed benefits, before deciding to approve such a source of funding.

Q. Do you have an opinion, based on your professional knowledge and experience, as to whether the widespread deployment of radio transmitting smart meters is a safe and prudent course of action, given the present state of knowledge concerning the effects of such radio transmissions upon biological processes?

A. I do. My belief is that such widespread deployment cannot be justified at this time based on the peer-reviewed research we have. I would say that universal deployment of such meters throughout our urban areas amount to an experiment on the people living in those areas, an experiment without the consent of the experimental subjects.

Q. Can you substantiate that point?

A. Yes. Earlier this year I was asked to write my concerns about the health hazards of smart meters. Forty five medical professionals and scientists, who together have authored hundreds of peer-reviewed articles on the effects of electromagnetic radiation, joined together with me in a statement expressing our views on the effects of low level radio frequency and microwave radiation in general and smart meter radiation in particular. That statement is attached to my testimony as Exhibit One.

Q. And can you tell us briefly what conclusions were expressed?

A. While smart meters are too new for there to be human health studies specifically on exposure from smart meters, there is a strong body of evidence that demonstrates a variety of adverse human health effects, including cancer and effects on brain and behavior, coming from exposure to radiofrequency radiation like that generated by wireless smart meters.

Q. To the best of your knowledge, what percentage of the general public could be called "electro-sensitive", i.e. people who experience more or less immediate symptoms when exposed to electromagnetic radiation, such as headaches, mental confusion, rapid heartbeat and so on?

A. While the evidence is incomplete for several reasons, most reports indicate that between 5 and 10% of the population show symptoms of electrical hypersensitivity.

Q. Is it possible that electro-sensitive people are like the canary in the mine? Or, more precisely, is it possible that the kind of electromagnetic fields that cause electro-sensitive people to experience immediate symptoms of distress, are also the kind of fields that are likely to cause long term illness to a much larger group of individuals who do not experience immediate symptoms?

A. Yes, this is not only possible but likely.

Q. So would it be fair to say that from a public health standpoint, protecting the most vulnerable among us might well be viewed not only as an act of compassion toward them but also have the effect of protecting the majority of the population from long term diseases like cancer or neurological diseases like Alzheimer's Disease?

A. This is true.

Q. Is there data on smart meters going back far enough to trace the long term effects of such meters on people?

A. No, but until more data becomes available we have to make inferences based on longer term data that we do have concerning use of cell phones and people living near to radio transmission towers. These studies show that increased radiofrequency exposure increases risk of cancer, and that the most vulnerable parts of the population are children and teenagers.

Q. Have you had occasion to testify previously about such effects?

A. Yes, in January, 2012, I testified concerning the effects of WiFi radiation on school children in the Oregon Public Schools. My legal testimony in that case is attached here as Exhibit Two.

Q. Can you give us a very brief summation in a few sentences as to your conclusions about the Wi-Fi study?

A. As with wireless smart meters, WiFi in schools exposes children constantly to radiofrequency radiation. As with smart meters, the specific health effects from exposure to WIFi have not been determined, but WiFi is radiofrequency radiation. Because children are more vulnerable than adults to radiofrequency radiation, as documented by studies from cell phone use and people living near to radio transmission towers, it is unwise to use WiFi in schools when a wired connection to the Internet does not increase exposure.

Q. Does an opt-out plan really solve the exposure risk you have been describing here and in your exhibits?

A. Not entirely. Not having a smart meter on one's own home will reduce the potentially harmful exposure, but the customer opting out is still going to be exposed to a whole blanket of electromagnetic radiation from the smart meters of immediate neighbors and from all the transmitting and receiving devices and repeaters the utility must install to allow all these meters to report their data, as well as other sources of radiofrequency radiation.

Q. If a smarter grid is necessary, what would be the best way to implement the necessary metering technology?

A. A properly designed system of wired smart meters using internet cable or fiber optics need not result in any elevated exposure to radio frequencies, but would still provide the utility with information about daily use.

Q. Detroit Edison is currently offering an opt-out meter that they call a “digital meter” which is the Itron smart meter with the radios turned off. We understand that it will store detailed usage information that a meter reader can download through a plug-in connection or through an optical port. Do you believe that this meter entirely solves the problem of RF exposure?

A. I am not familiar with the details of this meter and so cannot comment on whether or not it would be an entirely safe alternative. But, in principle, it should be possible to devise a safe digital meter that could communicate through a plug-in connection, or through hard-wired means.

Q. Is there anything else you would like to add to your testimony today?

A. Exposure to radiofrequency radiation has been shown to result in human disease, and we should take every step within reason to avoid increased exposure. All the benefits of a smart grid technology could be obtained with wired smart meters without increasing the risk of exposure and human disease. But at the very least everyone should have the opportunity to opt-out of having wireless smart meters placed on their home.

David O. Carpenter, M.D

Dated: November 13, 2012

DOREEN A. VanVORST

EXHIBIT ONE

2012 statement of David O. Carpenter, M.D. and
45 other scientists and health professionals
concerning hazards of radiation from 'smart meters'

Institute for Health and the Environment
State University of New York at Albany

We, the undersigned are a group of scientists and health professionals who together have coauthored hundreds of peer-reviewed studies on the health effects of electromagnetic fields (EMFs). We wish to correct some of the gross misinformation found in the letter regarding wireless "smart" meters that was published in the Montreal daily *Le Devoir* on May 24. Submitted by a group Quebec engineers, physicists and chemists, the letter in question reflects an obvious lack of understanding of the science behind the health impacts of the radiofrequency (RF)/microwave EMFs emitted by these meters.

The statement that "Thousands of studies, both epidemiological and experimental in humans, show no increase in cancer cases as a result of exposure to radio waves of low intensity…" is false (1). In fact, only a few such studies, case-control studies of mobile phone use, certainly not thousands, have reported no elevations of cancer, and most were funded by the wireless industry. In addition, these reassuring studies contained significant experimental design flaws, mainly the fact that the populations followed were too small, were followed for a too short a period of time and had used mobile phones for too short a period of time.

Non industry-funded studies have clearly demonstrated a significant increase in cancer cases among individuals who have suffered from prolonged exposure to low-level microwaves, transmitted notably by radio antennas. The effects were best documented in meta-analyses that have been published and that include grouped results from several different studies: these analyses consistently showed an increased risk of brain cancer among regular users of a cell phone who have been exposed to microwaves for at least ten years.

Brain Cancer Rates

Furthermore, the argument that brain cancer rates do not indicate an overall increase in incidence is not evidence that cell phones are safe: the latency for brain cancer in adults after environmental exposure can be long, up to 20-30 years. Most North Americans haven't used cell phones extensively for that long. The evidence of the link between long-term cell phone use and brain cancer comes primarily from Northern Europe, where cell phones have been commonly used since the 1990s.

Children are especially at risk. In May 2012, the U.K.'s Office of National Statistics reported a 50 percent increase in incidence of frontal and temporal lobe tumors in children between 1999 and 2009. This statistic is especially disturbing since in May 2011, after reviewing the published scientific literature regarding cancers affecting cell phone users, the International Agency for Research on Cancer (IARC) classified radiofrequency radiation as a 2B, possible human carcinogen. Despite the absence of scientific consensus, the evidence is sufficiently compelling for any cautious parent to want to reduce their loved one's exposure to RF/microwave emissions as much as possible, as recommended by various countries such as Austria, Belgium, Germany, Russia and the United Kingdom.

Electrosensitivity
Public fears about wireless smart meters are well-founded. They are backed by various medical authorities such as those of the Santa Cruz County (California) Public Health Department. These authorities are worried about the growing number of citizens who say they have developed electrohypersensitivity (EHS), especially since for many of them, the symptoms developed after the installation of such meters (it takes some time for most people to link the two events).

Since the turn of the millennium, people are increasingly affected by ambient microwaves due to the growing popularity of wireless devices such as cell phones and Wi-Fi Internet. Therefore, the mass deployment of smart grids could expose large chunks of the general population to alarming risk scenarios without their consent. According to seven surveys done in six European countries between 2002 and 2004, about 10% of Europeans have become electrosensitive, and experts fear that percentage could reach 50% by 2017. The most famous person to publicly reveal her electrosensitivity is Gro Harlem Brundtland, formerly Prime Minister of Norway and retired Director of the World Health Organization (WHO).

While there is no consensus on the origins and mechanisms of EHS, many physicians and other specialists around the world have become aware that EHS symptoms (neurological, dermatological, acoustical, etc.) seem to be triggered by exposure to EMF levels well below current international exposure limits, which are established solely on short-term thermal effects (2). Organizations such as the Austrian Medical Association and the American Academy of Environmental Medicine have recognized that the ideal way to treat of EHS is to reduce EMF exposure.

Therefore, caution is warranted because the growing variety of RF/microwave emissions produced by many wireless devices such as smart meters have never been tested for their potential biological effects.

Well-known bioeffects
While the specific pathways to cancer are not fully understood, it is scientifically unacceptable to deny the weight of the evidence regarding the increase in cancer cases in humans that are exposed to high levels of RF/microwave radiation.

The statement that "there is no established mechanism by which a radio wave could induce an adverse effect on human tissue other than by heating" is incorrect, and reflects a lack of awareness and understanding of the scientific literature on the subject. In fact, more than a thousand studies done on low intensity, high frequency, non-ionizing radiation, going back at least fifty years, show that some biological mechanisms of effect do not involve heat. This radiation sends signals to living tissue that stimulate biochemical changes, which can generate various symptoms and may lead to diseases such as cancer.

Even though RF/microwaves don't have the energy to directly break chemical bonds, unlike ionizing radiation such as X-rays, there is scientific evidence that this energy can cause DNA damage indirectly leading to cancer by a combination of biological effects. Recent publications have documented the generation of free radicals, increased permeability of the blood brain barrier allowing potentially toxic chemicals to enter the brain, induction of genes, as well as altered electrical and metabolic activity in human brains upon application of cell phone RF/microwaves similar to those produced by smart meters.

These effects are cumulative and depend on many factors including RF/microwave levels, frequency, waveform, exposure time, bioavailability between individuals and combination with other toxic agents.

Clear evidence that these microwaves are indeed bioactive has been shown by the fact that low-intensity EMFs have proven clinically useful in some circumstances. Pulsed EMFs have long been used to successfully treat bone fractures that are resistant to other forms of therapy. More recently, frequency-specific, amplitude-modulated EMFs have been found useful to treat advanced carcinoma and chronic pain.

High frequency EMFs such as the microwaves used in cell phones, smart meters, Wi-Fi and cordless ''DECT'' phones, appear to be the most damaging when used commonly. Most of their biological effects, including symptoms of electrohypersensitivity, can be seen in the damage done to cellular membranes by the loss of structurally-important calcium ions. Prolonged exposure to these high frequencies may eventually lead to cellular malfunction and death.

Furthermore, malfunction of the parathyroid gland, located in the neck just inches from where one holds a cell phone, may actually cause electrohypersensitivity in some people by reducing the background level of calcium ions in the blood. RF/microwave radiation is also known to decrease the production of melatonin, which protects against cancer, and to promote the growth of existing cancer cells.

Early warning scientists attacked

In recommending that the Precautionary Principle be applied in EMF matters, the European Environment Agency's Director Jacqueline McGlade wrote in 2009: "We have noted from previous health hazard histories such as that of lead in petrol, and methyl mercury, that 'early warning' scientists frequently suffer from discrimination, from loss of research funds, and from unduly personal attacks on their scientific integrity. It would be surprising if this is not already a feature of the present EMF controversy…" Such unfortunate consequences have indeed occurred.

The statement in the *Le Devoir* letter, "if we consider that a debate should take place, it should focus exclusively on the effects of cell phones on health", is basically an acknowledgement that there is at least some reason to be concerned about cell phones. However, while the immediate exposure from a cell phone is of much greater intensity than the exposure from smart meters, cell phone use is temporary.

Smart meters

Wireless smart meters typically produce atypical, relatively potent and very short pulsed RF/microwaves whose biological effects have never been fully tested. They emit these millisecond-long RF bursts on average 9,600 times a day with a maximum of 190,000 daily transmissions and a peak level emission two and a half times higher than the stated safety signal, as the California utility Pacific Gas & Electric recognized before that State's Public Utilities Commission. Thus people in proximity to a smart meter are at risk of significantly greater aggregate exposure than with a cell phone, not to mention the cumulative levels of RF/microwaves that people living near several meters are exposed to.

People are exposed to cell phone microwaves primarily in the head and neck, and only when they use their device. With smart meters, the entire body is exposed to the microwaves, which increases the risk of overexposure to many organs.

In addition to these erratic bursts of modulated microwaves coming from smart meters that are transferring usage data to electric, gas and water utilities, wireless and wired smart (powerline communication) meters are also a major source of ''dirty electricity'' (electrical interference of high frequency voltage transients typically of kilohertz frequencies). Indeed, some scientists, such as American epidemiologist Sam Milham, believe that many of the health complaints about smart meters may also be caused by dirty electricity generated by the « switching » power supply activating all smart meters. Since the installation of filters to reduce dirty electricity circulating on house wiring has been found to relieve symptoms of EHS in some people, this method should be considered among the priorities aimed at reducing potential adverse impacts. Indeed, the Salzburg State (Austria) Public Health Department confirms its concern about the potential public health risk when in coming years almost every electric wire and device will emit such transient electric fields in the kilohertz-range due to wired smart meters.

Rather be safe than sorry

The apparent adverse health effects noted with smart meter exposure are likely to be further exacerbated if smart appliances that use wireless communications become the norm and further increase unwarranted exposure.

To date, there have been few independent studies of the health effects of such sources of more continuous but lower intensity microwaves. However, we know after decades of studies of hazardous chemical substances, that chronic exposure to low concentrations of microwaves can cause equal or even greater harm than an acute exposure to high concentrations of the same microwaves.

This is why so many scientists and medical experts urgently recommend that measures following the Precautionary Principle be applied immediately — such as using wired meters — to reduce biologically inappropriate microwave exposure. We are not advocating the abolishment of RF technologies, only the use of common sense and the development and implementation of best practices in using these technologies in order to reduce exposure and risk of health hazards.

1. Scientific papers on EMF health effects
2. Explanation and studies on electrosensitivity
3. Governments and organizations that ban or warn against wireless technology

• David O. Carpenter, MD, Director, Institute for Health & the Environment, University at Albany, USA
• Jennifer Armstrong, MD, Past President, Canadian Society of Environmental Medicine, Founder, Ottawa Environmental Health Clinic, Ontario, Canada
• Pierre L. Auger, M. D., FRCPC, Occupational medicine, Multiclinique des accidentés 1464, Montreal, Quebec, Canada
• Fiorella Belpoggi, Director Cesare Maltoni Cancer Research Center, Ramazzini Institute, Bologna, Italy
• Martin Blank, PhD, former President, Bioelectromagnetics Society, Special Lecturer, Department of Physiology and Cellular Biophysics, Columbia University Medical Center, New York, USA

- Barry Breger, MD, Centre d'intégration somatosophique (orthomolecular medicine), Montreal, Quebec
- John Cline, MD, Professor, Institute for Functional Medicine, Federal Way, WA, USA, Medical Director, Cline Medical Centre, Nanaimo, BC, Canada
- Alvaro Augusto de Salles, PhD, Professor of Electrical Engineering, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
- Christos Georgiou, Prof. Biochemistry, Biology Department, University of Patras, Greece
- Andrew Goldsworthy, PhD, Honorary lecturer in Biology, Imperial College, London, UK
- Claudio Gómez-Perretta, MD, PhD, Director, Centro de Investigación, Hospital Universitario LA Fe, Valencia, Spain
- Livio Giuliani, PhD, Senior Researcher, National Insurance Institute (INAIL), Chief of Radiation and Ultrasounds Research Unit, Rome, Italy
- Yury Grigoriev, PhD, Chair Russian National Committee on Non-Ionizing Radiation Protection, Moscow, Russia
- Settimio Grimaldi, PhD, Director, Institute of Translational Pharmacology (Neurobiology and molecular medicine), National Research Council, Rome, Italy
- Magda Havas, PhD, Centre for Health Studies, Trent University, Canada
- Lennart Hardell, MD, Professor of Oncology, University Hospital, Örebro, Sweden
- Denis L. Henshaw, PhD, Professor of Physics, Head of The Human Radiation Effects Group, University of Bristol, UK
- Ronald B. Herberman, MD, Chairman of Board, Environmental Health Trust, and Founding Director emeritus, University of Pittsburgh Cancer Institute, USA
- Donald Hillman, PhD, Dairy Science, Professor Emeritus, Department of Animal Science, Michigan State University, USA
- Isaac Jamieson, PhD, Environmental Science (electromagnetic phenomena in the built environment), independent architect, scientist and environmental consultant, Hertfordshire, UK
- Olle Johansson, PhD, Professor of Neuroscience (Experimental Dermatology Unit), Karolinska Institute, Stockholm, Sweden
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- Don Maisch, PhD, Researcher on radiation exposure standards for telecommunications frequency, EMFacts Consultancy, Tasmania, Australia
- Erica Mallery-Blythe, MD, Emergency Medicine Physician, England
- Andrew A. Marino, MD, PhD, JD, Professor of Neurology, LSU Health Sciences Center, Shreveport, LA, USA
- Karl Maret, MD, M.Eng., President, Dove Health Alliance, Aptos, CA, USA
- Andrew Michrowski, PhD, Director, Planetary Association for Clean Energy, Ottawa, Canada
- Sam Milham, MD, former chief epidemiologist, Washington State Department of Health, USA
- Joel M. Moskowitz, PhD, Director, Center for Family and Community Health, School of Public Health, University of California, Berkeley
- Gerd Oberfeld, MD, Public Health Department, Salzburg State Government, Austria
- Mike O'Carroll, PhD, Professor Emeritus (Applied Mathematics), University of Sunderland, UK
- Jerry L. Phillips, PhD, Director, Center for Excellence in Science, Department of Chemistry and Biochemistry, University of Colorado, USA

• John Podd, PhD, Professor of Psychology (experimental neuropsychology), Massey University, New-Zeland
• William J. Rea, MD, thoracic and cardiovascular surgeon, founder of the Environmental Health Center, Dallas, Tx, USA
• Elihu D. Richter, MD, Professor, Hebrew University-Hadassah School of Public Health and Community Medicine, Jerusalem, Israel
• Leif G. Salford, MD, Senior Professor of Neurosurgery, Lund University, Sweden
• Nesrin Seyhan, MD, Founder and Chair of Biophysics, Medical Faculty of Gazi University, Turkey
• Cyril W. Smith, PhD, lead author of "Electromagnetic Man", retired from Electronic and Electrical Engineering, University of Salford, UK
• Morando Soffritti, MD, Scientific Director of the European Foundation for Oncology and Environmental Sciences "B. Ramazzini" in Bologna, Italy
• Antoinette "Toni" Stein, PhD, Collaborative on Health and the Environment (CHE-EMF Working Group), Co-Coordinator, Berkeley, CA, USA
• Stanislaw Szmigielski, MD, PhD Professor of Pathophysiology, Consulting Expert, former director of Microwave Safety, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
• Bradford S. Weeks, MD, Director, The Weeks Clinic, Clinton, WA, USA
• Stelios A. Zinelis, MD, Vice-President, Hellenic Cancer Society, Cefallonia, Greece

EXHIBIT TWO

Testimony of Dr. David O. Carpenter
Concerning health effects of WiFi System
In Portland, Oregon Public Schools

Testimony given under oath
December 20th, 2011
In United States District Court
District of Oregon
Portland Division

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United States District Court

District of Oregon

Portland Division

AHM, by and through
her Guardian *ad litem* and father,
David Mark Morrison, and
David Mark Morrison, individually,

v.

Portland Public Schools,

Defendant.

Civil Action No. 3:11-cv-00739-MO

Amended Declaration of
Dr. David O. Carpenter, M.D.

I, Dr. David O. Carpenter, M.D., under penalty of perjury pursuant to 28 U.S.C. § 1746, hereby make the following declaration in support of an injunction against Portland Public Schools' use of WI-FI:

1. I am a public health physician, educated at Harvard Medical School. My current title is Director of the Institute for Health and the Environment at the University at Albany and Professor of Environmental Health Sciences within the School of Public Health. Formerly, I was the Dean of the School of Public Health at the University of Albany and the Director of the Wadsworth Center for Laboratories and Research of the New York State Department of Health.

2. I served as the Executive Secretary to the New York State Powerlines Project in the 1980s, a program of research that showed children living in homes with elevated magnetic fields coming from powerlines suffered from an elevated risk of developing leukemia. After this I became the spokesperson on electromagnetic field (EMF) issues for the state during the time of my employment in the Department of Health. I have published several reviews on the subject and have edited two books.

3. I am a Co-Editor and a Contributing Author of the *BioInitiative: A Rationale for a Biologically-based Public Exposure Standard for Electromagnetic Fields (ELF and RF)*, www.bioinitative.org. It documents bioeffects, adverse health effects and public health conclusions about impacts of electromagnetic radiation (electromagnetic fields including extremely-low frequency ELF-EMF and radiofrequency /microwave or RF-EMF fields). The public health chapter from this report was subsequently published in a peer-reviewed journal.

4. Additionally, I am a Co-Author of *Setting Prudent Public Health Policy for Electromagnetic Field Exposures*, Reviews on Environmental Health, Volume 23, No 2, 2008, attached as Addendum A-2.

5. In addition, in 2009, I was invited to present to the President's Cancer Panel on the subject of powerline and radiofrequency fields and cancer, and have testified on this issue before the Unite States House of Representatives.

6. In sum, I am a public health physician, professor and former public health school Dean with expertise in electrophysiology, low-frequency electromagnetic fields bioeffects, and

radiofrequency (RF) and microwave (MW) radiation bioeffects.

7. WI-FI deploys pulse-modulated ("PM") microwave ("MW") radiation (within the larger RF radiation spectrum) with a carrier frequency that is similar to that used by a microwave oven: about 2.45 GHz. This is the "Agent". The 2.45 GHz frequency was chosen for the oven because of its wavelength and harmonic resonance with the water molecule, to ensure the most efficient absorption by living tissues and effective heating by way of the agitation of water at the molecular level. The pulse-modulation of a wave with lower frequencies in addition to the high-frequency carrier signal, increases the exposure complexity and in turn the bioeffects in an exposed population.

8. In the context of school development, WI-FI exposes building occupants including children and adults constantly from both computers and infrastructure antennas. Duration may be an even more potent contributing factor to RF/MW radiation bioeffects than exposure levels. Chronic, such as all-day, school exposure, is more likely than short and intermittent exposure, such as cell phone use, to produce harmful health effects, and is likely to do so at lower exposure levels.

9. Persons stationed close to school computers with WI-FI and especially those very near to any WI-FI infrastructure will receive considerably higher exposure than do others.

10. It is generally accepted within the relevant scientific community and has been established beyond any reasonable doubt that adverse human health effects occur at far lower levels of RF/MW radiation exposure than those that cause noticeable heating, particularly where the wavelength approaches body-part size and thus maximizes absorption, where the wavelength has resonance with the water molecule, where there is more complex, modulated wave, where there is chronic exposure duration, and where exposed persons lack the capacity voluntarily to remove themselves from radiation sources.

11. Some effects are shown to occur at several hundred thousand times below the FCC public exposure guidelines, which are set based on the fallacious assumption that there are no adverse health effects at exposures that do not cause easily measureable heating. FCC guidelines

also only apply to 30-minute public exposures; therefore do not even infer safety at durations >30 minutes, such as in a school setting.

12. Exposure to high-frequency RF and MW radiation and also the extreme low frequency (ELF) EM fields that accompany WI-FI exposure have been linked to a variety of adverse health outcomes. Some of the many adverse effects reported to be associated with and/or caused by ELF fields and/or RF/MW radiation include neurologic, endocrine, immune, cardiac, reproductive and other effects, including cancers.

13. Studies of isolated cells have shown that RF/MW exposures may cause changes in cell membrane function, cell communication, metabolism, activation of proto-oncogenes, and can trigger the production of stress proteins at exposure levels below FCC guidelines and also at and less than school WI-FI exposure levels and parameters. Resulting effects in cellular studies include without limitation DNA breaks and chromosome aberrations, cell death including death of brain neurons, increased free radical production, activation of the endogenous opioid system, cell stress and premature aging.

14. Human studies of comparable RF/MW radiation parameters show changes in brain function including memory loss, retarded learning, performance impairment in children, headaches and neurodegenerative conditions, melatonin suppression and sleep disorders, fatigue, hormonal imbalances, immune dysregulation such as allergic and inflammatory responses, cardiac and blood pressure problems, genotoxic effects like miscarriage, cancers such as childhood leukemia, childhood and adult brain tumors, and more.

15. There is consistent evidence for increased incidence of effects in individuals who live near to high-power short-wave, AM, FM and TV transmission towers. This is particularly relevant because, like WI-FI, radio-TV transmission towers give continuous, whole-body radiation, not just radiation to the head, constantly.

16. Since WI-FI transmitters, both infrastructural and on computers, are indoors, where children and teachers may be very close by, and since WI-FI, at 2.45 GHz, deploys a

wavelength, at ~12.2 cm or ~ 4.8 inches, more absorbable by children's and adults' bodies and brains than radio-TV wavelengths, the harmfulness of WI-FI radiation likely exceeds that of radio-TV towers.

17. Like second-hand smoke, EMF and RF/MW radiation involve complex mixtures, where different frequencies, intensities, durations of exposure(s), modulation, waveform and other factors are known to produce variable effects, often more harmful with greater complexity. Decades of scientific study have produced substantial evidence that EMF and RF/MW radiation may be considered neurotoxic, carcinogenic and genotoxic. Sources of fields and radiation, but are not limited to: power lines, navigational radar, cell phones, cordless phones [or Digitally Encoded Cordless Transmission Devices (D.E.C.T.) phones], cell towers, 'smart' meters and their grids or infrastructure, "smart" boards, meters and grids, WiMax and wireless internet (WI-FI).

18. The RF/MW radiation and low-frequency EMF science that currently exists includes tens of thousands of studies dating back to the 1920s. On the basis of this vast body of literature, many public health experts believe, myself included, that it is likely society will face epidemics of neurotoxic effects and degeneration, cancers and genotoxicity in the future, resulting from the extreme and mostly involuntary exposure to RF/MW radiation and EMFs. WI-FI radiation in schools exceeds natural background levels of microwave radiation by trillions of times. Thus, it is important that all of us restrict our use of cell phones, and be as free as possible from exposure to unnatural, background sources of MW radiation, particularly WI-FI.

19. In public health science, it is generally accepted fact that vulnerable subgroups exist within any human population. This is also recognized specifically for RF/MW radiation and fields. These groups include children, pregnant women, the elderly and those with preexisting illnesses and/or impairments. Children are more vulnerable to RF/MW radiation because of the susceptibility of their developing nervous systems. RF/MW penetration is greater relative to head size in children, who have a greater absorption of RF/MW energy in the tissues of the head at WI-FI frequencies.

Such greater absorption results because children's skulls are thinner, their brains smaller, and their brain tissue is more conductive than those of adults, and since it has a higher water content and ion concentrations. The Presidential Cancer Panel found that children 'are at special risk due to their smaller body mass and rapid physical development, both of which magnify their vulnerability to known carcinogens, including radiation.' http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf

20. FCC public RF/MW radiation exposure guidelines are based on the height, weight and stature of a 6-foot tall man, not children or adults of smaller stature. The guidelines do not take into account the unique susceptibility of growing children to exposures. Since children are growing, their rate of cellular activity and division is more rapid, and they are at more risk for DNA damage and subsequent cancers. Growth and development of the central nervous system is still occurring well into the teenage years, such that the neurological impairments predictable by the extant science may have great impact upon development, cognition, learning, and behavior. Prenatal exposure has been identified as a risk factor for childhood leukemia, and is associated with miscarriage. Children are largely unable to remove themselves from exposures to harmful substances in their environments. Their exposure is involuntary.

21. When WI-FI is in operation in a school, children and their parents have no choice but to allow the school to expose them to trillions of times higher microwave radiation than exists naturally on Earth at the same frequencies. Children and other building users are exposed to as much as 30-40 hours per week of constant, digitally encoded WI-FI signals from each wireless device and infrastructural antenna in a school building. Based upon a review of the Mount Tabor WI-FI Floor Plan, a given child is subject to direct signals from multiple WI-FI transmitters, including rooms full of students and teachers transmitting numerous laptop and other wireless signals. There is a major legal difference between an exposure that an individual chooses to accept and one that is forced upon a person, especially a dependent, who can do nothing about it.

22. WI-FI in the Portland Schools deploys similar PM MW radiation, at 2.45 and 5 GHz, to that of cell and cordless phones and their infrastructure. There is clear and strong evidence that intensive use of cell phones increases incidence of brain cancer, tumors of the auditory nerve, and cancer of the parotid gland, the salivary gland in the cheek by the ear. Cell and cordless phone radiation closely resembles that of WI-FI radiation exposure, except that WI-FI is more hazardous by way of frequency, duration, and the involuntary nature of exposure. While a cell or cordless phone is used only intermittently and primarily voluntarily, a WI-FI radiation microenvironment is constant in duration, with unavoidable radiation exposure even when nearby students are not actively using it. Because WI-FI radiation is essentially the same as, but more hazardous than, that for cell and cordless phones, there is every reason to understand that the health effects will be the same or worse, varying in relation to the total dose of radiation, and intensified by the constancy of duration. There is evidence from Scandinavian studies of cell phone usage that children who use cell phones are about five times more likely to develop brain cancer than if their usage starts as an adult. Thus, it is especially necessary to protect children from pulse-modulated MW radiation such as both cell phones and WI-FI deploy.

23. Based on a high degree of scientific certainty, Portland Public Schools' use of WI-FI is causing and will continue to cause AHM, other students, and school staff and faculty adverse health effects, and should be discontinued immediately. Educating by way of the Internet via cabled systems only decreases MW radiation exposure and is of minimal expense.

24. Having reviewed hundreds, possibly thousands, of studies in RF/MW radiation and ELF fields, published from decades ago to the present, I would provide you the following primary evidence, without limitation. Due to the active suppression of the RF/MW literature, some researchers in public health science are less aware of these studies. However, the forefront experts specializing in these areas, RF/MW radiation and ELF fields, recognize the certainties in this large body of scientific literature, which establishes without limitation that PM MW radiation with chronic duration is quite harmful to humans, particularly children, as well as to animals and plants.

25. It is not surprising that even as of 1990, the US Environmental Protection Agency ("EPA") had determined RF/MW radiation a "probable carcinogen". Now that we have much more confirming study in the interim, the conclusion is yet more certain. And when we focus on MW radiation, particularly pulse-modulated radiation, on long, non-intermittent duration and on more vulnerable subgroups such as children, we see that the cancer outcome is very certain, indeed. Amongst the epidemiologic studies showing cancer outcomes, the following are particularly strong:

a. Dode AC, Leao M, Tejo FdeAF, gomes ACR, Dode DC, Dode MC, Moreira CW, Condessa VA, Albinatti C and Calaffa WT. Mortality by neoplasia and cellular telephone base stations in the Belo Horizonte municipality, Minas Gerais State, Brazil. Sci Total Environ 409: 3649-3665:2011. This study shows higher rates of cancer in people living close to cell phone towers than for people living further away. Cell phone radiation is similar to but likely not as harmful as 2.45 GHz radiation from WI-FI. The exposure levels in this study are lower than those that Portland school building occupants receive from WI-FI.

b. Oberfeld G. Environmental Epidemiology Study of Cancer Incidence in the Municipalities of Hausmannstatten & Vasoldsberg (Austria), 2008. This government-commissioned study found significantly increased cancer risk relative to a lower-exposure reference category, 23x higher for breast cancer and 121x higher for brain tumors, with strong exposure-effect relations.

c. Michelozzi P, Capon A, Kirchmayer U, Forastiere F, Biggeri A, Barca A and Perucci CA. Adult and childhood leukemia near a high-power radiostation in Rome, Italy. Am J Epidemiol. 155: 1098-1103: 2002. The authors show that there is a significant elevation of childhood leukemia among residents living near to Vatican Radio, and that the risk declines with distance away from the transmitter. This is RF radiation in frequencies similar to that of WI-FI.

d. Ha M, Im H, Lee M, Kim HJ, Kim BC, Gimm YM and Pack JK. Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancer. Am J Epidemiol 166: 270-279: 2007. Leukemia and brain cancer in children in Korea were investigated in relation to residence within 2 km of AM radio transmitters. There was a significant elevation in rates of leukemia but not of brain cancer. WI-FI radiation is more harmful than AM.

e. Park SK, Ha M, Im HJ. Ecological study on residences in the vicinity of AM radio broadcasting towers and cancer death: preliminary observations in Korea. Int Arch Occup Environ Health. 2004 Aug:77(6):387-94. This study found higher mortality areas for all cancers and leukemia in some age groups in the area near the AM towers.

f. Hallberg O. Johansson O. Med Sci Monit 2004 Jul;10(7):CR336-40. Malignant melanoma of the skin – not a sunshine story! Increased incidence and mortality from skin melanoma are concluded to result from continuous disturbances of cell repair mechanisms by body-resonant EMFs from FM/TV networks.

g. Hallberg O. Johansson O. 2005. FM Broadcasting exposure time and malignant melanoma incidence, Electromagnetic Biology and Medicine 24;1-8. Age-specific incidence of malignant melanoma of the skin is related to FM broadcasting radiation at whole-body resonant frequencies. This is very relevant to children, since the smaller wavelengths of WI-FI are at resonant frequencies with dimensions of the human head, particularly the child's head.

h. Dolk H, Shaddick G, Walls P, Grundy C, Thakrar B, Kleinschmidt I, Elliot P. Cancer Incidence near radio and television transmitters in Great Britain. I – Sutton-Colfield transmitter, and II. Al high-power transmitters. Am J Epidemiol 1997; 145(1):1-9 and 10-17. In the first study, there was a statistically significant

increase in cancer; in the second, a small but significant increase in adult leukemia.

i. Hocking B, Gordon IR, Grain HL, Harfield GE. Cancer incidence and mortality and proximity to TV towers. Medical J of Australia. 165:601-605. At extremely low exposure levels, there was an association between increased childhood leukemia incidence and mortality and proximity to TV towers. TV radiation, in the VHF and UHF bands, is similar to but not as harmful as WI-FI radiation at 2.45 GHz.

j. Grayson JK. Radiation exposure, socioeconomic status, and brain tumor risk in the US Air Force: A nested case-control study. Am J Epidemiol 1996; 143:480-6. This study found an association between exposure to ELF and RF/MW radiation and brain tumors.

k. Szmigielski S. Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation. Sci Total Environ 1996;180:9-17. This study showed huge increases in leukemia and Non-Hodgkin's lymphomas. Though exposure levels are higher in this study than they would be with school WI-FI, it is possible that certain students or teachers stationed immediately next to the WI-FI infrastructure could receive comparable levels in radiation peaks.

26. Additional studies show neurologic, immune, endocrine, reproductive and cardiac, adverse health effects from low-dose, chronic exposure to RF/MW radiation in humans:

a. Papageorgiou CC, Hountala CD, Maganioti AE, Kyprianou MA, Rabavilas AD, Papadimitriou GN, Capsalis CN. Effects of WI-FI signals on the p300 component of event-related potentials during an auditory hayling task. J Integr Neurosci 2011 Jun;10(2):189-202. This study concludes that WI-FI exposure may exert gender-related alterations on neural activity.

b. Altpeter ES, Roosli M et al. Effect of Short-wave magnetic fields on sleep quality and melatonin cycle in humans: The Schwarzenburg shut-down study. Bioelectromagnetics 27:142-150, 2006. Sleep quality improved and melatonin excretion increased when the transmitter was shut down.

c. Abelin T et al. Sleep disturbances in the vicinity of the short-wave braoadcast transmitter Schwarzenburg. Somnologie 9:203-209, 2005. There is strong evidence of a causal relationship between operation of a short-wave radio transmitter and sleep disturbances in the surrounding population.

d. Hutter HP et al. Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. Occup Environ Med 2006;63:307-313, 2006. There was a significant relation of some symptoms, especially headaches, to measured power density, as well as effects on wellbeing and performance.

e. Preece AW, Georgious AG, Duunn EJ, Farrow SC. Occup Environ Med 2007 Jun;64(6):402-8. Compared to control village, there were highly significant differences in the reporting of migraine, headache and dizziness military and cell phone antenna systems.

f. Buchner K, Eger, H. Changes of clinically important neurotransmitters under the influence of modulated RF fields – a long-term study under real-life conditions. Umwelt-Medizin-Gesellschaft 24(1):44-57, 2011. There is clear evidence of health-relevant effects, including increase in adrenaline/noradrenaline, subsequent decrease in dopamine from a new MW-emitting base station. During counterregulation, trace amine PEA decreased and remained decreased. Clinically documented increases in sleep problems, cephalgia, vertigo, concentration problems and allergies followed the onset of new microwave transmissions.

g. Eliyahu I, Luria R, Hareuveny R, Margaliot M, Neiran N and Shani G . Effects of radiofrequency radiation emitted by cellular telephones on the cognitive functions of humans. Bioelectromagnetics 27: 119-126: 2006. A total of 36 human subjects were exposed to PM MW and were tested on four distinct cognitive tasks. Exposure to the left side of the brain slows left-hand response time in three of the four tasks.

h. Barth A, Winker R, Ponocny-Seliger E, Mayrhofer W, Ponocny I, Sauter C and Vana N. Occup Environ Med 65: 342-345: 2008. A meta-analysis for neurobehavioural effects due to electromagnetic field exposure emitted by GSM mobiile phones. The authors looked at 19 studies of cognitive function in cell phone users, and found in the meta-analysis that there is evidence for a decreased reaction time, altered working memory and increased number of errors in exposed persons.

i. Augner C, Hacker GW, Oberfeld G, Florian M, Hitzl W, Hutter J and Pauser G. Effects of exposure to base station signals on salivary cortisol, alpha-amylase and immunoglobulin A. Biomed Environ Scie 23: 199-207: 2010. This was a human experimental study with exposure to PM MW radiation wherein immune indicators were monitored after five 50-minute sessions. The researchers found dose-dependent changes in cortisol and alpha-amylase.

j. Avendano C, Mata A, Sanchex Sarimiento CA and Doncel GF. Use of laptop computers connected to internet through WI-FI decreases human sperm motility and increases sperm DNA fragmentation. Fert Steril, 2012, In press. In this study human sperm were exposed to WI-FI from a laptop, and were found to show reduced motility after a 4-hour exposure. The results are consistent with other publications (see Agarwal et al., Fert Steril 89: 124-128: 2008) that reported that those who use cell phone regularly have reduced sperm count.

k. Baste V, Riise T and Moen BE (2008) Int J Epidemiol 23: 369-377: 2008. Radiofrequency electromagnetic fields: male infertility and sex ratio of offspring. This is a study of Norwegian Navy personnel chronically exposed to RF fields on the job. The rates of infertility were related to level of exposure in a dose-dependent fashion.

27. Many toxicologic and other animal studies, of which the following are but a few, support conclusions of cancer, genotoxicity, neurotoxicity and other health outcomes from RF/MW radiation.

a. Sinha R. Chronic non-thermal exposure of modulated 2450 MHz microwave radiation alters thyroid hormones and behavior of male rats. Int. J. Radiation Biol. 84:6:505-513, 2008. This study of 2.45 GHz at levels and durations comparable to and less than those of school WI-FI concluded that the radiation was sufficient to alter the levels of thyroid hormone as well as emotional reactivity compared to controls.

b. Nittby H, Grafstrom G, Tian DP, Malmgren L, Brun A, Persson BRR, Salfor LG and Eberhardt J. Bioelectromagnetics 29: 219-232: 2008. This study showed cognitive impairment in rats after long-term exposure to PM MW radiation. This is study of rats shows that after 2 hours per week for 55 weeks there was impaired memory for objects in exposed as compared to sham animals.

c. Kimmel S et al. Electromagnetic radiation: Influences on honeybees (Apis mellifera). A significant difference between non-exposed and fully irradiated bees was the result of the influence of high-frequency PM RF/MW radiation.

d. Panagopoulos DJ et al. Bioeffects of mobile telephony radiation in relation to its intensity or distance from the antenna. Int. J Radiat Biol, 86;(5):345-357, 2010. The PM MW radiations at 900 and 1800 MHz decreased the reproductive capacity by cell death induction, with an increased bioactivity "window" at 10

uW/cm2, and still evident down to 1 uW/cm2.

e. Everaert J, Bauwens D. A possible effect of electromagnetic radiation from mobile phone base stations on the number of breeding house sparrow (passer domesticus). Electromagnetic Biology and Medicine, 26:63-72, 2007. Long-term exposure to higher-level low-intensity PM MW radiation negatively affects the abundance or behavior of House Sparrows in the wild.

f. Magras I, Xenos T. RF Radiation-Induced Changes in the Prenatal Development of Mice. Bioelectromagnetics 18:455-461, 1997. Near almost 100 TV and FM broadcast transmitters, with exposure levels between 0.168 uW/cm2 and 1.053 uW/cm2, found in the more exposed groups testicular damage and decreasing size of litters to irreversible infertility.

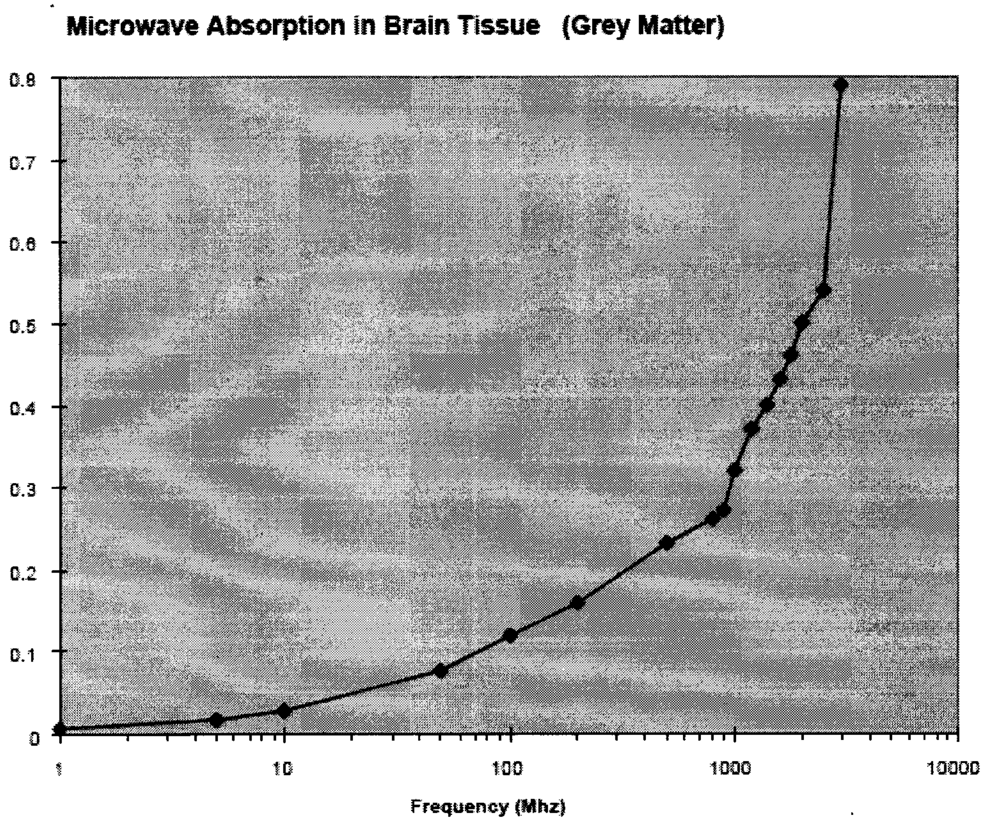
g. Balmori A. Electromagnetic pollution from phone masts. Effects on wildlife, Pathophysiology 2009. This large review of wildlife effects concludes, "pulsed telephony microwave radiation can produce effects on nervous, cardiovascular, immune and reproductive systems," including damage to the nervous system by altering EEG and changes to the blood-brain barrier, disruption of the circadian rhythms (sleep-wake) by interfering with the pineal gland and hormonal imbalances, changes in heart ate and blood pressure, impairment of health and immunity towards pathogens, weakness, exhaustion, growth problems, problems in building the nest or impaired fertility, embryonic development, hatching percentage, genetic and developmental problems, problems of locomotion, promotion of tumors and more.

28. Exposure thresholds for harmful effects are lowered in human populations and individuals when duration is increased. Due to the variability of thresholds for harmful effects both in the population and within the individual, there is no exposure power density that is safe. The School's WI-FI deploys arguably the worst possible frequency of 2.45 GHz, that of the

microwave oven, worst because it is most absorbable by the brain and most resonant with the water molecule, such that:

a. absorption-per-exposure is maximized, dramatically lowering effects thresholds for population and individual effects; and

b. water molecules in tissues and cells are highly agitated.



Curry, Ph.D., *Wireless LANs in the schoolroom*

29. This above graph, from physicist William Curry PhD's presentation *Wireless LANs in the Schoolroom*, shows how absorption in brain tissue (grey matter) increases exponentially toward the ultra-high frequency (UHF) area of the microwave oven and WI-FI.

30. In the case of the Portland Schools, the additional, unused but still deployed carrier frequency of 5 GHz would likely increase absorption in other, smaller organs, such as the thyroid.

31. The graph also illustrates the problem with the drive of the wireless industry toward ever higher frequencies within the cm microwave band. While nearly all the lower frequency bands have already been allocated by the FCC for specific types of radio transmissions, and transmission of ever more information content on any given channel requires greater bandwidth, each new deployment undermines further the integrity of the population's health. Engineers who design these systems have no training that would qualify them to consider the effects on biologic systems, which is why public health scientists need to be called in to policymaking *prior to* contracting and deployment, not after the fact.

32. The following studies explain the mechanisms of interaction between RF/MW radiation and biologic systems at the cellular level.

a. The cell membrane recognition process -- which includes signal transduction and 'heat-shock protein' release -- was first discerned by Litovitz and his co-workers at Catholic University of America in the mid-1990s. Below are a few citations that make the point.

i. Litovitz, T., C. Montrose, et al. (1994). "Superimposing spatially coherent electromagnetic noise inhibits field induced abnormalities in developing chick embryos." *Bioelectromagnetics* **15**(2): 105-113.

ii. DiCarlo, A., J. Farrell, et al. (1998). "A simple experiment to study electromagnetic field effects: Protection induced by short term exposures to 60 Hz magnetic fields." *Bioelectromagnetics* **19(8)**: 498-500.

iii. Penafiel, L., T. Litovitz, et al. (1997). "Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929

cells." *Bioelectromagnetics* **18**(2): 132-141.

iv. Dicarlo, A. L., Michael T. Hargis, L. Miguel Penafiel, Theodore A. Litovitz, A. (1999). "Short-term magnetic field exposures (60Hz) induce protection against ultraviolet radiation damage." *International journal of radiation biology* **75**(12): 1541-1549.

v. Litovitz, T., C. Montrose, et al. (1990). "Amplitude windows and transiently augmented transcription from exposure to electromagnetic fields." *Bioelectromagnetics* **11**(4): 297-312.

vi. Litovitz, T., M. Penafiel, et al. (1997). "The role of temporal sensing in bioelectromagnetic effects." *Bioelectromagnetics* **18**(5): 388-395.

vii. Litovitz, T., L. Penafiel, et al. (1997). "Role of modulation in the effect of microwaves on ornithine decarboxylase activity in L929 cells." *Biolectomagnetics* 18: 132-141.]

viii. Litovitz, T., D. Krause, et al. (1993). "The role of coherence time in the effect of microwaves on ornithine decarboxylase activity." *Bioelectromagnetics* **14**(5): 395-403.

b. Cell membrane reaction is lipid peroxidation.

i. Serban, M. and V. Ni (1994). "Lipid peroxidation and change of plasma lipids in acute ischemic stroke." *Romanian journal of internal medicine= Revue roumaine de médecine interne* **32**(1): 51.

ii. Vileno, B., S. Jeney, et al. (2010). "Evidence of lipid peroxidation and protein phosphorylation in cells upon oxidative stress photo-generated by fullerols."*Biophysical chemistry*.

iii. Maaroufi, K., E. Save, et al. (2011). "Oxidative stress and prevention of the adaptive response to chronic iron overload in the brain of young adult rats exposed to a 150 kilohertz electromagnetic field." *Neuroscience*.

iv. Nelson, S. K., S. K. Bose, et al. (1994). "The toxicity of high-dose superoxide dismutase suggests that superoxide can both initiate and terminate lipid peroxidation in the reperfused heart." *Free Radical Biology and Medicine* **16**(2): 195-200.

v. Alvarez, J. G. and B. T. Storey (1989). "Role of glutathione peroxidase in protecting mammalian spermatozoa from loss of motility caused by spontaneous lipid peroxidation." *Gamete research* **23**(1): 77-90.

vi. Devasagayam, T., K. Boloor, et al. (2003). "Methods for estimating lipid peroxidation: An analysis of merits and demerits." *Indian journal of biochemistry & biophysics* **40**(5): 300-308.

c. Free-Radical Damage:

i. Ozgur, E., G. Güler, et al. (2010). "Mobile phone radiation-induced free radical damage in the liver is inhibited by the antioxidants n-acetyl cysteine and epigallocatechin-gallate." *International journal of radiation biology*(00): 1-11.

ii. Gutteridge, J. and X. C. Fu (1981). "Enhancement of bleomycin-iron free radical damage to DNA by antioxidants and their inhibition of lipid peroxidation." *FEBS letters* **123**(1): 71.

d. mRNA:

i. Yan, J. G., M. Agresti, et al. (2009). "Qualitative Effect on mRNAs of Injury-Associated Proteins by Cell Phone Like Radiation in Rat Facial Nerves. *Electromagnetic Biology and Medicine* **28**(4): 383-390.

ii. Yan, J. G., M. Agresti, et al. (2008). "Upregulation of specific mRNA levels in rat brain after cell phone exposure." *Electromagnetic Biology and Medicine* **27**(2): 147-154.

iii. Simbürger, E., A. Stang, et al. (1997). "Expression of connexin43 mRNA in adult rodent brain."*Histochemistry and cell biology* **107**(2): 127-137.

iv. Chen, J., H. C. He, et al. (2010). "Effects of Pulsed Electromagnetic Fields on the mRNA Expression of RANK and CAII in Ovariectomized Rat Osteoclast-Like Cell." *Connective Tissue Research* **51**(1): 1-7.

e. Epigenetic changes.... environmentally induced genetic change:

i. Migliore, L. and F. Copped (2009). "Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases." *Mutation Research/Fundamental and Molecular*

Mechanisms of Mutagenesis **667**(1-2): 82-97.

ii. Currenti, S. (2009). "Understanding and Determining the Etiology of Autism." *Cellular and Molecular Neurobiology* **30**(2): 161-171.

f. Micronuclei formation:

i. Tice, R. R., G. G. Hook, et al. (2002). "Genotoxicity of radiofrequency signals. I. Investigation of DNA damage and micronuclei induction in cultured human blood cells." *Bioelectromagnetics*, **23**(2): 113-126.

ii. Lerchl, A. (2009). "Comments on "Radiofrequency electromagnetic fields (UMTS, 1,950 MHz) induce genotoxic effects in vitro in human fibroblasts but not in lymphocytes" by Schwarz et al. (Int Arch Occup Environ Health 2008: doi: 10.1007/s00420-008-0305-5)." *Int Arch Occup Environ Health* **82**(2): 275-278.

iii. Vijayalaxmi and T. J. Prihoda (2009). "Genetic damage in mammalian somatic cells exposed to extremely low frequency electro-magnetic fields: a meta-analysis of data from 87 publications (1990-2007)." Int J Radiat Biol **85**(3): 196-213.

iv. Sannino, A., M. Sarti, et al. (2009). "Induction of adaptive response in human blood lymphocytes exposed to radiofrequency radiation." *Radiat Res* **171**(6): 735-742.

g. DNA repair disruption:

i. Brusick, D., R. Albertini, et al. (1998). "Genotoxicity of radiofrequency radiation. DNA/Genetox Expert Panel." *Environ*

Mol Mutagen **32**(1): 1-16.

ii. Belyaev, I. Y., E. Markova, et al. (2009). "Microwaves from UMTS/GSM mobile phones induce long-lasting inhibition of 53BP1/gamma-H2AX DNA repair foci in human lymphocytes."*Bioelectromagnetics* **30**(2): 129-141.

iii. Sun, L. X., K. Yao, et al. (2006). "[Effect of acute exposure to microwave from mobile phone on DNA damage and repair of cultured human lens epithelial cells in vitro]." *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* **24**(8): 465-467.

h. Immune response suppression:

i. Lyle, D. B., P. Schechter, et al. (1983). "Suppression of T-lymphocyte cytotoxicity following exposure to sinusoidally amplitude-modulated fields." *Bioelectromagnetics* **4**(3): 281-292.

ii. Elekes, E., G. Thuroczy, et al. (1996). "Effect on the immune system of mice exposed chronically to 50 Hz amplitude-modulated 2.45 GHz microwaves." *Bioelectromagnetics* **17**(3): 246-248.

iii. DABALA, D., D. SURCEL, et al. (2008). "Oxidative and Immune Response in Experimental Exposure to Electromagnetic Fields." *Electromagnetic field, health and environment: proceedings of EHE'07*: 105.

iv. Surcel, D., D. Dabala, et al. (2009). "Free Radicals, Lipid Peroxidation and Immune Response in Experimental Exposure to Electromagnetic Fields." *Epidemiology* **20**(6): S118.

Conclusions

33. To understand the seriousness of this Agent of PM RF/MW radiation in interaction with populations and individuals, we need to consider some basic facts in addition to the many relevant and reliable studies above. For example, where shortwave, AM. FM, TV and cell phone infrastructure frequencies are demonstrated to be harmful, as they consistently are shown to be at low intensities with long duration, then, all other factors being equal, MW radiation at 2.45 GHz will likely be more harmful yet, due to its higher absorption-per-exposure and water molecule resonance. Increasing the constancy and length of exposure toward the maximum of occupational and 24-7 durations will lower the threshold for effects in populations and individuals. Complex radiation microenvironments with pulse-modulated wave and multiple sources, such as are deployed in WI-FI-equipped schools, are more harmful than a single, isolated MW radiation exposure at the same power density and duration. There are only a few of the many studies of RF/MW radiation infrastructure such as base stations that fail to show their studied effect. However, even were the reverse true, i.e., if there existed greater number than those that do show adverse effects, it is the case that positive studies (those that show adverse effects) hold more weight than negative studies (those that show no effect).

34. The FCC-appointed guideline-setting Commission, ASTM-IEEE, in 1991 referred in its conclusions to RF/MW radiation, the Agent, as a 'Hazard,' specifically setting a 'Hazard Threshold.' It has been discovered that, even amongst the 120 studies chosen by the Committee to prove the validity of its Hazard Threshold, there were 15 studies that concluded adverse effects at levels *lower* than the Hazard Threshold, thus disproving its validity. Three of these studies actually showed adverse effects at less than 10 percent of the Hazard Threshold. Thus the guidelines have no credibility.

35. The large body of scientific literature moreover redundantly proves this Agent to be a hazard. The media-promulgated notion that the relevant scientific studies are inconsistent and inconclusive is false and misleading. Chronic exposure to PM MW radiation harms every individual in a population in some ways, even if these are not always detectable by the individual or consciously attributed to the responsible RF/MW radiation sources. This Agent injures some individuals into a condition in which symptoms will be more easily retriggered with subsequent exposure. And for *a priori* susceptible individuals and those using electronic medical devices, it can respectively exacerbate the extant medical conditions and disrupt medical device operation, even to the point of death. Bassen 1997 discusses the hundreds of excess deaths, even at that time, from wireless communications radiation. See also *Radiofrequency Interference with Medical Devices*, IEEE Engineering in Medicine and Biology Magazine 17(3):111-114(1998), http://ewh.ieee.org/soc/embs/comar/interfer.htm.

36. For these reasons, WI-FI must be banned from school deployment.

37. I will receive no compensation for my testimony beyond out-of-pocket expenses.

Dated this 20th day of December, 2011.

David O. Carpenter

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Schenectady, New York 12303

Positions Held:
Director, Institute for Health and the Environment
University at Albany
Professor, Environmental Health Sciences
School of Public Health, University at Albany
5 University Place, A217, Rensselaer, NY 12144

Education:

1959	B.A., Harvard College, Cambridge, MA	
1964	M.D., Harvard Medical School, Boston, MA	

Positions Held:

9/61-6/62	Research Fellow, Department of Physiology, University of Göteborg, Sweden with Professor Anders Lundberg
7/64-6/65	Research Associate, Department of Physiology, Harvard Medical School, Boston, MA under the direction of Dr. Elwood Henneman
7/65-2/73	Neurophysiologist, Laboratory of Neurophysiology, National Institutes of Mental Health, Dr. Edward V. Evarts, Chief, Assistant Surgeon, USPHS, currently a Reserve Officer in the USPHS.
2/73-3/80	Chairman, Neurobiology Department Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, Bethesda, MD
3/80-9/85	Director, Wadsworth Center for Laboratories and Research, New York State Department of Health, Albany, NY
9/85-1/98	Dean, School of Public Health, University at Albany
9/85-Pres.	Professor, Departments of Environmental Health Sciences and Biomedical Sciences, School of Public Health, University at Albany.
9/85-7/98	Research Physician, Wadsworth Center for Laboratories and Research, New York State Department of Health, Albany, NY
1/98-1/05	Adjunct Professor in the Center for Neuropharmacology & Neuroscience, Albany Medical College, Albany, NY
2001-Pres.	Director, Institute for Health and the Environment, University at Albany, SUNY, Rensselaer, NY. The Institute was named a Collaborating Center of the World Health Organization in 2011.
2005-Pres.	Senior Fellow, Alden March Bioethics Institute, Albany Medical College/Center, Albany, New York

Editor-in-Chief: Cellular and Molecular Neurobiology, 1981 - 1987
Editorial Advisor: Cellular and Molecular Neurobiology, 1987 - Present
Editorial Boards: Journal of Public Health Management and Practice, 1995 - 2002
International Journal of Occupational Medicine & Environmental Health 1996 – Present

Journal of Alzheimer's Disease, Associate Editor,2007-2009
Reviews in Environmental Health; 2008-present
International Archives of Occupational and Environmental Health; 2009-present.
Journal of Environmental and Public Health, 2009-present.
Environmental Health Perspectives, 2010-present

National and International Committees:

1978, 1981	Physiology Study Section (Ad hoc member)
1979-1985	NIH International Fellowship Study Section
1974-1981	Member, Steering Committee of the Section on the Nervous System, American Physiological Society (Chairman of the Committee, 9/76-4/80)
1981-1989	Member, USA National Committee for the International Brain Research Organization
1985-1986	Committee on Electric Energy Systems of the Energy Engineering Board, National Research Council
1986-1987	Member, Neurophysiology Peer Panel for the National Aeronautics and Space Administration
1987-1989	Member, Science Advisory Council of the American Paralysis Association
1987-1990	Advisory Panel for the Electric Energy System Division, U.S. Department of Energy
1985-1993	Committee #79, National Council on Radiation Protection and Measurements
1986-1997	Member, Legislative and Education Committees, Association of Schools of Public Health
1989-1994	Member, Neuroscience Discipline Working Group, Life Sciences Division of the NASA
1994, 1995	Federation of American Societies for Experimental Biology Consensus Conference on FY 1995 Federal Research Funding
1994-1997	Member, Legislative Committee of the Association of Schools of Public Health
1997	Member, Executive Committee of the Association of Schools of Public Health
1997-2000	National Advisory Environmental Health Sciences Council of the National Institutes of Health
1998-Pres.	Member, U.S. Section of the Great Lakes Science Advisory Board of the International Joint Commission
2000-Pres.	Member, Board of Directors, Pacific Basin Consortium for Hazardous Waste Health and Environment; Treasurer, 2001-2004, 2008-pres; Chair, 2004-2008
2001-2008	United States Co-Chair, Workgroup on Ecosystem Health of the Science Advisory Board of the International Joint Commission
2002-2003	Member, Committee on the Implications of Dioxin in the Food Supply, The National Academies, Institute of Medicine
2003-2008	Member, United States Environmental Protection Agency, Children's Health Protection Advisory Committee
2003-Pres.	Chair, Advisory Committee to the World Health Organization and National Institute of Environmental Health Sciences on collaborative activities.
2007-2011	Chair, Workgroup on Risks vs. Benefits of Fish Consumption, Science Advisory Board, International Joint Commission.

State and Local Committees:

1980-1987 Executive Secretary, New York State Power Lines Project
1985-1989 Board of Scientific Advisors, Institute of Basic Research, OMRDD, N.Y.
1986-1989 Member, Steering Committee, Health Policy and Administrative Consortium of the Capital District
1991-1992 Member, Connecticut Academy of Sciences and Engineering Committee on Electromagnetic Field Health Effects
1991-1992 Member, Board of Directors of the Capital District Chapter of the Alzheimer's Disease and Related Disorders Association, Inc.
1991-1992 Member, State Task Force for the Reform of Middle Level Education in NY State
1992-1993 Member, State Needs Task Force on Health Care and Education
1987-1998 Delegate-at-Large, New York State Public Health Association
1991-1995 Member, Board of Directors of the Capital District Amyotrophic Lateral Sclerosis Association
1994 Chair, Council of Deans, University at Albany, SUNY
1997-2008. Member, Board of Directors, (Chair 1998-2004) Albany-Tula Inc.: A Capital Region Alliance
2000-Pres. Member, Board of Directors, Healthy Schools Network, Inc.
2000-2003 Member, Medical Advisory Board, Hepatitis C Coalition, New York
2000-2004 Member, Environmental Protection Agency /National Association of State Universities and Land Grant Colleges Task Force
2001-2008 Member, Board of Directors, Environmental Advocates of New York
2004-2007 Member, Ad Hoc Advisory Group on Brownfield Cleanup Standards
2005-Pres. Member, Schooling Chefs Curriculum Advisory Board
2005-2008 Member, Board of Directors, Citizens Environmental Coalition
2006-2009 Member, Board of Directors, Marine Environmental Research Institute
2007-2009 Member, New York State Renewable Energy Task Force

Honors, Awards and Fellowships:

1959 B.A. awarded magna cum laude. Thesis entitled "Metamorphosis of visual pigments: A study of visual system of the salamander, Ambystoma tigrinum" (Thesis advisor, Professor George Wald)
Elected to Phi Beta Kappa and to Sigma Xi

1964 M.D. awarded cum laude for a thesis in a special field. Thesis entitled "Electrophysiological observations on the importance on neuron size in determining responses to excitation and inhibition in motor and sensory systems" (Thesis advisor, Dr. Elwood Henneman)

1964 Awarded the Leon Resnick Prize given to a Harvard Medical School graduate showing promise in research

1970 Awarded the Moseley Traveling Fellowship for study in England (Fellowship declined)

1971 Invited as Visiting Professor of Physiology, Centro de Investigacion y de Estudios Avanzados, del Institute Politecnico Nacional, Mexico 14, D.F., Mexico, for 3 months

1982, 1986 Visiting Professor of Physiology, Department of Physiology, Kyushu
1987 University, Fukuoka, Japan, for a period of three months each

1989 Awarded Jacob Javits Neuroscience Investigator Award from the National Institute of Neurological and Communicative Diseases and Stroke

1999 Awarded Homer N. Calver Award from the American Public Health Association for studies in environmental health.

2001 Awarded 2001 Academic Laureate from the University at Albany Foundation.

2010 Awarded the Albion O. Bernstein, M.D. Award in recognition of an outstanding contribution to public health and the prevention of disease though lifelong research of environmental health hazards and for limitless devotion to medical education by the Medical Society of the State of New York.

Federal Grants Held: (Principal Investigator Only)

1980-1983 United States Air Force, "Mechanisms of Radiation-Induced Emesis in Dogs", $76,847 total direct costs.

1982-1988 National Institute of Health, "Mechanisms of Desensitization at Central Synapses", $464,786 total direct costs.

1984-1986 Defense Nuclear Agency, "Mechanisms of Radiation-Induced Emesis in Dogs@, $330,504 total direct costs.

1986-1996 National Institute of Health, "Mechanisms of Excitatory Amino Acids Actions and Toxicity", 1986-1989 $231,848 total direct costs; 1990-1996 $562,926 total direct costs.

1989-1993 National Institute of Health, "Mechanisms of Lead Neurotoxicity" $373,576 total direct costs

1990-1995 National Institute of Environmental Health Sciences, Superfund Basic Research Program, "Multidisciplinary Study of PCBs and PCDFs at a Waste Site", D.O. Carpenter, P.I. $5,783,419 total direct costs.

1995-2001 Fogarty International Center, National Institutes of Health, International Training Program in Environmental and Occupational Health. ACentral/Eastern European Environ/Occup Training Program@, D.O. Carpenter, P.I. $657,520 total costs.

1995-2001 National Institute of Environmental Health Sciences, Superfund Basic Research Program, "Multidisciplinary Study of PCBs," D.O. Carpenter, P.I. $12,653,709 total direct costs.

1998-1999 Environmental Protection Agency, AIndoor Air Risk at Akwesasne - Pilot Project@, D.O. Carpenter, P.I. $9,996 total costs.

2000-2002 Association Liaison Office for University Cooperation in Development, ACooperative Program in Environmental Health between the Institute of Public Health at Makerere University, Kampala, Uganda and the School of Public Health, University at Albany, USA@, D.O. Carpenter, P.I. $96,432 total costs.

2001-2007 Fogarty International Center, National Institutes of Health, International Training Program in Environmental and Occupational Health. AMultidisciplinary Environmental Health Training@, D.O. Carpenter, P.I. $850,000 total costs.

2006-2011 Pakistan-US Science and Technology Cooperative Program (US National Academy of Sciences). "Association of particulate matter with daily morbidity in

an urban population," D.O. Carpenter, P.I., $391,104 total costs.

2009-2013 Exploratory Center on Minority Health and Health Disparities in Smaller Cities. Project 2: Environmental contaminants and reproductive health of Akwesasne Mohawk women. $387,825 for year 1. D.O. Carpenter, Co-PI.

2010-2013 Department of the Army, "Gulf War Illness: Evaluation of an Innovative Detoxification Program: D.O. Carpenter, P.I., $636,958 total costs.

2010-2013 Higher Education for Development of the United States Agency for International Development, "Drinking Water Supply, Sanitation, and Hygiene Promotion : Health Interventions in Two Urban Communities of Kampala City and Mukono Municipality, Uganda". D. O. Carpenter, P.I., $299,736 total costs.

2011-2016 National Institute of Environmental Health Sciences (1RO1ES019620), "Protecting the health of future generations: Assessing and preventing exposures." PK Miller, FA von Hippel, CL Buck and DO Carpenter, Co-P.I.s, $471,521 for the period 8/08/11-4/30/12, $2,354,871 for the period 2011-2016.

Research Interests:

- Exposure to persistent organic pollutants and risk of diabetes, cardiovascular disease, and hypertension.
- Cognitive and behavioral effects of environmental contaminants on children (IQ, ADHD) and older adults (dementias, Parkinson's Disease and ALS).
- Ionizing and non-ionizing radiation biology.
- Effects of air pollution on respiratory and cardiovascular function.

Other Professional Activities:

Host, The Public Radio Health Show (a 30 min public health information show carried on 170+ stations nationwide), plus the Armed Forces Radio Network and Voice of America, 1985-2001. Authored a biweekly health column in The Troy Record, a local newspaper, 1997-1999.

Major Peer-Reviewed Publications:

1. Carpenter, D.O., Lundberg, A. and Norrsell, U. Effects from the pyramidal tract on primary afferents and on spinal reflex actions to primary afferents. Experientia, 18:337, 1962.
2. Carpenter, D.O., Engberg, I. and Lundberg, A. Presynaptic inhibition in the lumbar cord evoked from the brain stem. Experientia, 18:450, 1962.
3. Carpenter, D.O., Lundberg, A. and Norrsell, U. Primary afferent depolarization evoked from the sensorimotor cortex. Acta Physiol. Scand., 59:126-142.
4. Carpenter, D.O., Engberg, I., Funkenstein, H. and Lundberg, A. Decerebrate control of reflexes to primary afferents. Acta Physiol. Scand., 59:424-437, 1963.
5. Carpenter, D.O., Engberg, I. and Lundberg, A. Differential supraspinal control of inhibitory and excitatory actions from the FRA to ascending spinal pathways. Acta Physiol. Scand., 63:103-110, 1965.

6. Henneman, E., Somjen, G.G. and Carpenter, D.O. Excitability and inhibitibility of motoneurons of different sizes. J. Neurophysiol., 28:599-620, 1965.
7. Henneman, E., Somjen, G.G. and Carpenter, D.O. Functional significance of cell size in spinal motoneurons. J. Neurophysiol., 28:560-580, 1965.
8. Somjen, G.G., Carpenter, D.O. and Henneman, E. Selective depression of alpha motoneurons of small size by ether. J. Pharmacol., 148:380-385, 1965.
9. Somjen, G., Carpenter, D.O. and Henneman, E. Response of motoneurons of different sizes to graded stimulation of supraspinal centers of the brain. J. Neurophysiol., 28:958-965, 1965.
10. Carpenter, D.O., Engberg, I. and Lundberg, A. Primary afferent depolarization evoked from the brain stem and the cerebellum. Arch. Ital. Biol., 104:73-85, 1966.
11. Carpenter, D.O. and Henneman, E. A relation between the threshold of stretch receptors in skeletal muscle and the diameter of axons. J. Neurophysiol., 29:353-368, 1966.
12. Carpenter, D.O. Temperature effects on pacemaker generation, membrane potential, and critical firing threshold in Aplysia neurons. J. Gen. Physiol., 50:1469-1484, 1967.
13. Chase, T.N., Breese, G., Carpenter, D., Schanberg, S. and Kopin, I. Stimulation-induced release of serotonin from nerve tissue. Adv. Pharmacol., 6A:351-364, 1968.
14. Carpenter, D.O. and Alving, B.O. A contribution of an electrogenic Na^+ pump to membrane potential in Aplysia neurons. J. Gen. Physiol., 52:1-21, 1968.
15. Olson, C.B., Carpenter, D.O. and Henneman, E. Orderly recruitment of muscle action potentials. Arch. Neurol., 19:591-597, 1968.
16. Carpenter, D.O. Membrane potential produced directly by the Na^+ pump in Aplysia neurons. Comp. Biochem. Physiol., 35:371-385, 1970.
17. Carpenter, D.O. and Gunn, R. The dependence of pacemaker discharge of Aplysia neurons upon Na^+ and Ca^{++}. J. Cell. Physiol., 75:121-127, 1970.
18. Kraus, K.R., Carpenter, D.O. and Kopin, I. R. Acetylcholine-induced release of norepinephrine in the presence of tetrodotoxin. J. Pharmacol. Exp. Therap., 73:416-421, 1970.
19. Barker, J.L. and Carpenter, D.O. Thermosensitivity of neurons in the sensorimotor cortex of the cat. Science, 169:597-598, 1970.
20. Carpenter, D.O., Hovey, M.M. and Bak, A. Intracellular conductance of Aplysia neurons and squid axon as determined by a new technique. Intl. J. Neurosci., 2:35-48, 1971.
21. Carpenter, D.O., Breese, G., Schanberg, S. and Kopin, I. Serotonin and dopamine: Distribution and accumulation in Aplysia nervous and non-nervous tissues. Int. J. Neurosci., 2:49-56, 1971.
22. Hovey, M.M., Bak, A.F. and Carpenter, D.O. Low internal conductivity of Aplysia neuron somata. Science, 176:1329-1331, 1972.
23. Carpenter, D.O. Electrogenic sodium pump and high specific resistance in nerve cell bodies of the squid. Science, 179:1336-1338, 1973.
24. Carpenter, D.O. and Rudomin, P. The organization of primary afferent depolarization in the isolated spinal cord of the frog. J. Physiol. (Lond.), 229:471-493, 1973.
25. Shain, W., Green, L.A., Carpenter, D.O., Sytkowski, A.J. and Vogel, Z. Aplysia acetylcholine receptors: Blockage by and binding of α-bungarotoxin. Brain Res., 72:225-240, 1974.
26. Pierau, Fr.-K., Torrey, P. and Carpenter, D.O. Mammalian cold receptor afferents: Role of an electrogenic sodium pump in sensory transduction. Brain Res., 73:156-160, 1974.

27. Saavedra, J.M., Brownstein, M.J., Carpenter, D.O. and Axelrod, J. Octopamine: Presence in single neurons in Aplysia suggests neurotransmitter function. Science, 185:364-365, 1974.
28. Willis, J.A., Gaubatz, G.L. and Carpenter, D.O. The role of the electrogenic sodium pump in modulation of pacemaker discharge of Aplysia neurons. J. Cell. Physiol., 84:463-472, 1974.
29. Brownstein, M.J., Saavedra, J.M., Axelrod, J., Zeman, G.H. and Carpenter, D.O. Coexistence of several putative neurotransmitters in single identified neurons of Aplysia. Proc. Natl. Acad. Sci. (USA), 71:4662-4665, 1975.
30. Carpenter, D.O. and Gaubatz, G.L. Octopamine receptors on Aplysia neurons mediate hyperpolarization by increasing membrane conductance. Nature, 252:483-485, 1974.
31. Pierau, Fr.-K., Torrey, P. and Carpenter, D.O. Afferent nerve fiber activity responding to temperature changes of the scrotal skin of the rat. J. Neurobiol., 38:601-612, 1975.
32. Carpenter, D.O. and Gaubatz, G.L. H_1 and H_2 histamine receptors on Aplysia neurons. Nature, 254:343-344, 1975.
33. Carpenter, D.O., Hovey, M.M. and Bak, A.F. Resistivity of axoplasm. II. Internal restivity of giant axons of squid and Myxicola. J. Gen. Physiol., 66:139-148, 1975.
34. Zeman, G.H. and Carpenter, D.O. Asymmetric distribution of aspartate in ganglia and single neurons of Aplysia. Comp. Biochem. Physiol., 52C:23-26, 1975.
35. Pierau, Fr.-K., Torrey, P. and Carpenter, D.O. Effect of ouabain and potassium-free solution on mammalian thermosensitive afferents in vitro. Pflugers Arch., 359:349-356, 1975.
36. Swann, J.W. and Carpenter, D.O. The organization of receptors for neurotransmitters on Aplysia neurons. Nature, 258:751-754, 1975.
37. Yarowsky, P.J. and Carpenter, D.O. Aspartate: distinct receptors on Aplysia neurons. Science, 192:806-809, 1976.
38. Foster, K.R., Bidinger, J.M. and Carpenter, D.O. The electrical resistivity of aqueous cytoplasm. Biophys. J., 16:991-1001, 1976.
39. Carpenter, D.O., Greene, L.A., Shain, W. and Vogel, Z. Effects of eserine and neostigmine on the interaction of α-bungarotoxin with Aplysia acetylcholine receptors. Mol. Pharmacol., 12:999-1006, 1976.
40. Saavedra, J.M., Ribas, J., Swann, J. and Carpenter, D.O. Phenylethanolamine: A new putative neurotransmitter in Aplysia. Science, 195:1004-1006, 1977.
41. Carpenter, D.O., Swann, J.W. and Yarowsky, P.J. Effect of curare on responses to different putative neurotransmitters in Aplysia neurons. J. Neurobiol., 8:119-132, 1977.
42. Yarowsky, P.J. and Carpenter, D.O. GABA mediated excitatory responses on Aplysia neurons. Life Sci., 20:1441-1448, 1977.
43. Willis, J.A., Myers, P.R. and Carpenter, D.O. An ionophoretic module which controls electroosmosis. J. Electrophysiol. Tech., 6:34-41, 1977.
44. Yarowsky, P.J. and Carpenter, D.O. Receptors for gamma-aminobutyric acid (GABA) on Aplysia neurons. Brain Res., 144:75-94, 1978.
45. Carpenter, D.O., Gaubatz, G., Willis, J.A. and Severance, R. Effects of irradiation of Aplysia pacemaker neurons with 20 MeV electrons. Rad. Res., 76:32-47, 1978.
46. Yarowsky, P.J. and Carpenter, D.O. A comparison of similar ionic responses to gamma-aminobutyric acid and acetylcholine. J. Neurophysiol., 41:531-541, 1978.
47. Blum, B., Auker, C.R. and Carpenter, D.O. A head holder and stereotaxic device for the rattlesnake. Brain Res. Bull., 3:271-274, 1978.

48. Swann, J.W., Sinback, C.N. and Carpenter, D.O. Dopamine-induced muscle contractions and modulation of neuromuscular transmission in Aplysia. Brain Res., 157:167-172, 1978.
49. Swann, J.W., Sinback, C.N. and Carpenter, D.O. Evidence for identified dopamine motor neurons to the gill of Aplysia. Neurosci. Lett., 10:275-280, 1978.
50. Kebabian, P.R., Kebabian, J.W. and Carpenter, D.O. Regulation of cyclic AMP in heart and gill of Aplysia by the putative neurotransmitters, dopamine and serotonin. Life Sci., 24:1757-1764, 1979.
51. Carpenter, D.O. Interchangeable association of neurotransmitter receptors with several ionophores. Brain Res. Bull., 4:149-152, 1979.
52. Pellmar, T.C. and Carpenter, D.O. Voltage-dependent calcium current induced by serotonin. Nature, 277:483-484, 1979.
53. Ruben, P.C., Swann, J.W. and Carpenter, D.O. Neurotransmitter receptors on gill muscle fibers and the gill peripheral nerve plexus in Aplysia. Canad. J. Physiol. Pharmacol., 57:1088-1097, 1979.
54. Pellmar, T.C. and Carpenter, D.O. Serotonin induces a voltage-sensitive calcium current in neurons of Aplysia californica. J. Neurophysiol., 44:423-439, 1980.
55. Parver, L.M., Auker, C. and Carpenter, D.O. Choroidal blood flow as a heat dissipating mechanism in the macula. Am. J. Ophthamol., 89:641-646, 1980.
56. Mell, L.D., Jr. and Carpenter, D.O. Fluorometric determination of octopamine in tissue homegenates by high-performance liquid chromatography. Neurochem. Res., 5:1089-1096, 1980.
57. Braitman, D.J., Auker, C.R. and Carpenter, D.O. Thyrotropin-releasing hormone has multiple actions in cortex. Brain Res., 194:244-248, 1980.
58. Meszler, R.M., Auker, C.R. and Carpenter, D.O. Fine structure and organization of the infrared receptor relay, the lateral descending nucleus of the trigeminal nerve in pit vipers. J. Comp. Neurol., 196:571-584, 1981.
59. Auker, C.R., Parver, L.M., Doyle, T. and Carpenter, D.O. Choroidal blood flow: I. Ocular tissue temperature as a measure of flow. Arch. Opthal., 100:1323-1326, 1982.
60. Parver, L.M., Auker, C., Carpenter, D.O. and Doyle, T. Choroidal blood flow: II. Reflexive control in the monkey. Arch. Opthal., 100:1327-1330. 1982.
61. Hori, N., Auker, C.R., Braitman, D.J. and Carpenter, D.O. Lateral olfactory tract transmitter: Glutamate, aspartate or neither? Cell. Mol. Neurobiol., 1:115-120, 1981.
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PREVIOUS DEPOSITIONS AND TESTIMONY (past seven years):

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John Edward Martinez and Gladys Yolanda Martinez vs. Entergy Corporation et al., deposed for the plaintiffs, 16 April 2008. Julie Jacobs, Attorney. 504-566-1704.

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Fannie Wayne et al. vs. Pharmacia Corporation et al., testified for the plaintiffs, 31 March-1 April, 2009. John E. Norris, Attorney. 205-541-7759.

Clement Passariello, et al., vs. CL&P, et al.; William Korzon, et al., vs. CL&P, et al.; Louis Gherlone et al., vs. CL&P, et al.; and William Ho, et al., vs. CL&P et al., deposed for the plaintiffs, 13 April 2009. Benson A. Snaider, Attorney. 203-777-6426.

Before the Pennsylvania Public Utility Commission, docket No A-2009-2082652, et al. Testified on behalf of the Saw Creek Estates Community Association, 2 September 2009. Paul M. Schmidt, Attorney. 215-569-2800 x161.

James Alford et al. v. Kuhlman Corporation, et al., pending in the USDC, Southern District of Mississippi, Deposed for plaintiffs, 20 August 2009. Shiela Bossier, Attorney. 601-352-5450

Fannie Wayne et al. v. Pharmacia Corporation. Deposed for plaintiffs, 23 September 2009, Timothy C. Davis, Attorney. 205-327-9115.

Before the Minnesota Public Utilities Commission in the matter of the route permit application by Great river energy and Xcel Energy for a 345 kV transmission line from Brookings County, South Dakota to Hampton, Minnesota. Testified for plaintiffs, 16 December

2009. Paula Maccabee, Attorney. 651-775-7128.

Highland Lakes Estates et al.v. Republic Services of Florida et al., Deposed for the plaintiffs, 23 April 2010. John W. Frost II, Attorney. 863-533-8985.

Zina G. Bibb, et al. v Monsanto Company et al. Deposed for plaintiffs, 28 April 2010. W. Stuart Calwell, Attorney, 304-343-4323.

Highland Lakes Estates et al., v. Republic Services of Florida et al., Testified for the plaintiffs, 13 May 2010.

Nora Williams, et al., v. City of Jacksonville, et al. Deposed for the plaintiffs.15 July 2010. Samuel W. Wethern, Attorney.

Ronald Cybart et al., Michael Campanelli, and Donald and Theresa Shea, et al.v. CL&P. Deposed for the plaintiffs. 15 July 2011. Benson A. Snaider, Attorney.

Maria Snoops vs. Lyon Associates, Inc. and Insurance Co of the state of Pennsylvania. Deposed for the plaintiff, 1 November 2011. Matthew J. Witteman, Attorney. 415-363-3106.

John Edward Martinez and Gladys Yolanda Martinez v. Entergy Corporation, et al., Deposed for the plaintiff, 19 December 2011. J. Patrick Connick, Attorney. 504-347-4535.

CARPENTER DEPO
EXHIBIT 18

2012 WL 6964347 (D.Conn.) (Expert Deposition)
United States District Court, D. Connecticut.

Judy Prescott BARNETT, Plaintiff, v. CONNECTICUT LIGHT & POWER COMPANY, Northeast Utilities, Northeast Utilities Service Company and the United Illuminating Company., Defendants.

No. 311-cv-1037(VLB).
April 6, 2012.

Deposition of David O. Carpenter, M.D.

Name of Expert: David O. Carpenter, M.D.
Area of Expertise: Medical & Surgical >> Hospital
Area of Expertise: Medical & Surgical >> Public Health
Area of Expertise: Medical & Surgical >> Toxicology
Representing: Plaintiff
Jurisdiction: D.Conn.

Appearances.

Attorneys for Plaintiff, Gabriel North Seymour, Esq., 200 Route 126, Falls Village, CT 06031, Whitney North Seymour, Esq., 425 Lexington Avenue, Room 1721, New York, New York 10017.

Attorneys for Defendants Connecticut Light & Power Company, Northeast Utilities, Northeast Utilities Service Company, Anthony M. Fitzgerald, Esq., Carmody & Torrance, 195 Church Street, PO Box 1950, New Haven, CT 06509-1950.

DEPOSITION of DAVID O. CARPENTER, M.D., held on the 6th day of April 2012, commencing at 9:51 a.m. at the Environmental Health Sciences East Campus, 5 University Place, Rensselaer, New York, before Jeanne O'Connell, Registered Professional Reporter and Notary Public in and for the State of New York.

(Defendant's Exhibit A marked for identification.)

VIDEOGRAPHER: My name is Mati Kiin. I'm the certified legal video specialist for Western Mass Legal Video. Our business address is 5 Stockbridge Road, West Stockbridge, Massachusetts 01266. Today's date is April 6th, 2012, and the time is approximately 9:52.

This is the deposition of David O. Carpenter, M.D., in the matter of Judy Prescott Barnett, plaintiff, versus Connecticut Light & Power Company, Northeast Utilities, Northeast Utilities Service Company, and the United Illuminating Company, defendants, in the United States District Court District of Connecticut, civil action number 3:11-CV-1037(VLB).

This deposition is being taken at the State University of New York at Albany Environmental Health Sciences East Campus, located at 5 University Place, Rensselaer, New York 12144, on behalf of the defendant.

Our court reporter today is Jeanne O'Connell.

Will counsel now please state their appearances. And then the court reporter will administer the oath.

MR. FITZGERALD: Thank you. I am Anthony Fitzgerald of Carmody & Torrance, representing the defendants, Connecticut

Light & Power Company, Northeast Utilities Service Company, and Northeast Utilities.

And I should mention that attorney Bethany Appleby, who represents United Illuminating Company, will not be here today but has authorized us to go forward in her absence.

MR. SEYMOUR: My name is Whitney Seymour, Jr. I represent the plaintiff, Judy Barnett, along with my colleague, Gabrielle Seymour, who's sitting to my left.

DAVID O. CARPENTER, M.D., after first having been duly sworn, was examined and testified as follows:

EXAMINATION BY MR. FITZGERALD:

Q. Good morning, Dr. Carpenter.

A. Good morning.

Q. I'm going to hand you what's already been marked as Defendants' Carpenter A, which is a notice for this deposition, and ask you if you have had occasion to review it before you came here.

A. Yes, I have.

Q. And if we can turn directly to Exhibit A, there is a list of items that I asked you to bring with you. I would like to run through the list briefly and see what, if anything, you brought that is responsive to each request.

The first item is time records, diaries, and bills relating to your work on this case.

A. Yes. I don't have any time records because I haven't kept any. I was asked to prepare a report for a flat sum, which has been received, and I do have the receipt of that here somewhere.

Q. Well, that's -- I know what you're referring to. You don't need to hunt for that.

Do you normally keep time records?

A. I normally keep time records, yes.

In reality, other than the preparation of the report, I have done nothing except meeting with the plaintiff's attorneys yesterday for about three hours, and then reviewing some of the documents early this morning.

Q. All right. Let's move on to item two, correspondence with counsel.

A. I have copies of that right here.

MR. SEYMOUR: Make two comments about that.

One, you'll see a perfect example of Yankee frugality in the fact that the correspondence has been printed out on previously used papers. It has scrap paper often on the reverse, sometimes on the face. An X has been put through those. And if you make copies, those portions should be disregarded.

I should also mention that, to the extent there are any documents now privileged as work product, that is attorney work product, they are not included. I will make a disclosure of those to you, identification of those.

MR. FITZGERALD: Rather than use up video and stenographic time to discuss that, I do -- I would like to discuss that with you when we go off the record. And we may need to make a statement on the record when we come back.

BY MR. FITZGERALD:

Q. Item number three is correspondence with others who have examined or treated Judith Prescott Barnett.

Do you have that?

A. I have had no personal correspondence with anyone. I have been provided copies of reports of her treating physicians. I have those here. I suspect you have those as ready. But I have had no personal interaction with any of the other treatment physicians.

Q. Fine. Number four, your complete file in connection with any consultation with services rendered to any legal counsel representing Judy Prescott Barnett, including documents that you prepared, documents that you received from counsel, and documents that you reviewed in connection with the assignments.

And I see you have a file of --

A. Well, these are really not that. I believe everything is in there. Copies of my reports are included there, I believe, are they not?

MR. SEYMOUR: The material provided by counsel is included in there.

MR. FITZGERALD: You mean it's listed there.

MR. SEYMOUR: Yeah. No. I think there are copies of them.

MR. FITZGERALD: All right. Okay.

BY MR. FITZGERALD:

Q. And what else is in the green binders?

A. There are some scientific references that I am sure we will talk about.

Q. Okay.

A. There is this documentation of payment, which you said you didn't need, and things like the summary order, and then the notice of deposition, and another copy of the summary order. This is a copy of my statement.

Q. Yes, okay.

A. Which you have.

Q. Yes.

A. And the rest of these are the reports from the treating physicians.

Q. Could I see what you're referring to as the summary order, please?

A. It's this.

MR. FITZGERALD: This is the order of the Second Circuit Court of Appeals.

MR. SEYMOUR: That's in the other case and does not belong here.

MR. FITZGERALD: Well, it's in the previous Barnett case.

MR. SEYMOUR: Uh-huh.

THE WITNESS: I also brought an updated copy of my curriculum vitae, which you didn't ask for but you're welcome to have, if you want.

MR. FITZGERALD: Sure, thank you.

BY MR. FITZGERALD:

Q. And in your declaration you mention that you have reviewed the amended complaint.

Do you have that? Or maybe that was the declaration in the first case.

In any event, do you have with you a copy of any complaint that you have reviewed in connection with your opinion that you've rendered in this case?

A. I do have -- this is not an amended complaint, but I have that listing of...

MR. SEYMOUR: That's the material that we supplied after Mrs. Barnett's deposition, which is also in the other pile.

THE WITNESS: And I do have this, which is part of the amended complaint.

MR. FITZGERALD: An excerpt, okay. All right.

Before we go off the record so I can take a look at these things, I think we missed one thing when the witness was sworn in, and that is to note that the deposition is being taken pursuant to the Rules of Civil Procedure, to stipulate to the sufficiency of the notice and the authority of the notary, and to acknowledge that the witness will read and sign the deposition, but that we have agreed to an extension of the usual time for him to do that so that it will be either 30 days from the date he receives the deposition transcript or 60 days from today, whichever is later.

Off the record, please.

VIDEOGRAPHER: The time now is approximately 10:02 and we are now going off the record.

(Off the record.)

(Defendants' Exhibits B through I marked for identification.)

VIDEOGRAPHER: The time now is approximately 10:12 and we are now back on the record.

MR. SEYMOUR: During the off-the-record discussion a few minutes ago, plaintiff's counsel produced copies that we made at Staples last night of studies that Dr. Carpenter discussed with us during conference yesterday, and which he has referred to in connection -- referred to in connection with preparation for this deposition. Copies are now in the hands of Mr. Fitzgerald, representing the defendants.

Also, in connection with the disclosure of communications, we have withheld, I believe, two e-mails that relate to exchange -- the transmission of a draft of the doctor's report in this case, and I think also an e-mail which he asked us if we'd like to see it. We said yes.

Those are privileged, expressly privileged under the amended 26 rule that drafts are no longer producible. And I think that gets us up to date.

Any question?

MR. FITZGERALD: No. Not for you.

MR. SEYMOUR: I'd be glad to help.

MR. FITZGERALD: All right. Let's see. Where shall we begin? Are there copies around of these documents I just marked, or do I now have the only one?

MR. SEYMOUR: I think if I were to have the only ones, maybe if you'll describe them or let us look at them we can tell you.

MR. FITZGERALD: Well, we can try and go from there.

BY MR. FITZGERALD:

Q. Exhibit B, Dr. Carpenter, appears to be your engagement letter; is that correct?

A. Yes. That is correct.

Q. And there's a list of enclosures in the letter?

A. Yes.

Q. And the second -- one of them has an asterisk next to it.

What does that say?

A. Says, the transcript of Mrs. Barnett's deposition conducted on September 12th, 2011 by the power companies' attorneys along with notes prepared by us identifying your principal testimony regarding health conditions.

MR. SEYMOUR: That was sent electronically, and so you may not even have a printout.

THE WITNESS: I did not print it out.

BY MR. FITZGERALD:

Q. Why is the asterisk there?

A. The asterisk says, transcript to be sent by e-mail for ease of reference.

Q. Okay. And then Exhibit C is -- appears to be an e-mail to you from Mr. Seymour, which refers to an attached electronic copy of the deposition.

A. Correct.

Q. And so you received that electronic copy but you did not print it out.

A. That's correct.

Q. Did you read it on the screen?

A. Yes. I can't say I read it super carefully, but I certainly skimmed it.

MR. SEYMOUR: I think there's also a reference to that being a summary enclosed. And you've already got that, right?

MR. FITZGERALD: Actually, if I need your help I'll ask for it.

MR. SEYMOUR: All right. I'm trying to be helpful. Okay. I will withdraw all further help unless asked.

BY MR. FITZGERALD:

Q. Now, Defendants' D appears to be a set of references to Mrs. Barnett's deposition. It's entitled principal medical conditions mentioned by Judy Barnett during her deposition on September 12th, 2011 paraphrased from transcript.

Can you identify that document, please?

A. Yes. That is a correct description of this.

Q. And how did you use that document?

A. Well, this is basically a summary prepared by the plaintiff's attorneys of the diseases that Mrs. Barnett reported.

I used this in preparing my report because some of these diseases can be related to exposure to electromagnetic fields, others cannot.

Q. Tell me, please, what Exhibit E is.

MR. SEYMOUR: May we see a copy, please?

THE WITNESS: Well, this is an excerpt from the amended complaint, again, prepared by the plaintiff's attorneys. And it provides a list of concerns about her physical and mental state.

BY MR. FITZGERALD:

Q. And did you receive and review a copy of the full complaint?

A. I do not believe that I did. If I did, I did not review it carefully.

Q. Here is Defendants' Exhibit F, another of the documents that you just produced. Please explain to us what that is.

A. Yes. This is a statement of the magnetic field levels in her home as a function of time.

Q. And were you provided with any other similar documents?

A. With measurements of magnetic fields?

Q. Of magnetic fields.

A. Not like this. Not with real time measurements, no.

Q. All right. That was my question.

And tell us what Defendants' Exhibit G is.

A. I apologize for the figures on the page.

This is a report of a neuropsychiatric evaluation of Mrs. Barnett conducted January of this year by a, I believe, a psychologist from the University of Arizona, by Alex Hishaw, M.D., who is an assistant professor of neurology and psychiatry at the

University of Arizona health sciences center.

Q. When did you receive that?

A. On March 27th of this year.

Q. And so you received that document after you prepared the witness declaration?

A. Yes. That's correct. That was prepared sometime earlier.

Q. Let's just identify that.

Do you recognize Exhibit I as a copy of your witness declaration of this case?

A. That's correct. And this was dated October 21st, 2011.

Q. Just so we get everything identified before we move on, Exhibit H is a copy of your updated curriculum vitae?

A. That is correct.

MR. FITZGERALD: We're up to J. Would you please mark these reports, the set of documents, J-1, 2, etc.

VIDEOGRAPHER: The time now is approximately 10:21 and we are going off the record.

(Defendant's Exhibits J-1 through J-8 marked for identification.)

(Off the record.)

VIDEOGRAPHER: The time now is approximately 10:28 a.m. and we are now back on the record.

MR. FITZGERALD: The reporter has just marked Defendants' J-1 through J-8, which are copies of some articles that Mr. Seymour had handed to me at the beginning of the deposition.

Q. Do you have a set of these articles that you can refer to?

A. Yes, I do.

Q. First I'd like to ask you: Do you refer to any of these articles in your declaration that's been marked as Exhibit H?

A. No. I believe I did not refer to any of those articles, and I have not submitted to you copies of the articles I did refer to, although I have most of them with me.

Q. All right. I'm interested right now in let's call them the J articles. You did not refer to them in your declaration.

When did you first look at any of these articles in connection with your work on this case?

A. Well, many of those articles are very recent publications that only appeared in 2012. Some of them are older publications that I actually searched for and found yesterday when discussing with the plaintiff's attorneys some of the diseases reported by Mrs. Barnett.

There are some that are really subsequent to the psychiatrist's report, that was also 2012, with which altered my understanding of the diseases that Mrs. Barnett has.

I had been proceeding under the assumption that she had Alzheimer's disease, which actually was her self-report. It is very

clear she does not have Alzheimer's disease.

And that suggests very strongly that many of the symptoms that she has are, in fact, cases of electrical hypersensitivity, a syndrome that has been described for some period of time, and for which I have a large file of reports, but one for which I had some reservations about the weight of the evidence, whether it really was cause and effect of electromagnetic fields.

And I think my own view on the subject changed dramatically when the paper on the top that you have there appeared, which I saw for the first time only about two or three weeks ago. This is the first really blinded, well-done evaluation of a person under controlled circumstances in the department of neurology that was able to document the appearance of headache and other symptoms in relation to whether or not fields were on when the subject did not know whether or not they were on.

Q. Doctor, in your declaration, Exhibit H, do you mention electro hypersensitivity?

A. No. I did not specifically mention electro hypersensitivity. At the time I wrote that declaration, I had been actually a little berated by some in the more advocacy community in publicly expressing my feeling that the whole existence of that disease was not firmly established.

My position at that time is very closely reflected in the World Health Organization report, which I think probably is the second document in there, which acknowledge --

MR. SEYMOUR: J-2, I believe.

A. Yes. It has been described by many people, but until the J-1 report, all attempts to take a person that reported these rather non-specific symptoms into a laboratory where the individual did not know whether or not they were exposed, those studies had not been conclusive.

Now, in my report, I do make a statement near the end of my report that there are other reported health effects that are less well documented than the two that I focused on, which was the relationship between exposure and cancer, and the relationship between exposure and Alzheimer's disease, which, accepting Mrs. Barnett's self-diagnosis, I was assuming was the disease she suffered from.

Q. Would you point out to me the language in Exhibit H that you just referred to?

A. Under paragraph 28, the second sentence says, "There's evidence for biological effects on other organ systems but some uncertainty as to the degree to which these effects constitute a health hazard."

Q. Okay. I am looking now at Defendants' J-2, which you identified as emanating from the World Health Organization. It's World Health Organization facts sheet number 296.

And it uses the term "EHS." It is short for electromagnetic --

A. Electro hypersensitivity.

Q. Electromagnetic hypersensitivity.

Page 2 it says, "EHS is characterized by a variety of non-specific symptoms that differ from individual to individual. The symptoms are certainly real and can vary widely in their severity. Whatever its cause, EHS can be a disabling problem for the affected individual. EHS has no clear diagnostic criteria, and there is no scientific basis to link EHS symptoms to EMF exposure."

Now, putting together your earlier testimony, I take it that at the time that you wrote this declaration in October of 2011 that was your opinion.

A. That's correct.

I have followed the literature on EHS. I have a whole folder of papers. But, again, the -- it was exactly my opinion that these people -- I have phone calls quite frequently from individuals who report suffering from EHS.

The question is, is this a real disease, or are these people that have psychiatric problems, or are these people that are ill for other reasons and they simply focus on the magnetic fields.

So, I shared the opinion that's reflected in that World Health Organization report. Yes, there are many people that suffer this array of symptoms. It's very much like chronic-fatigue syndrome, Gulf War illness syndrome, multiple fibromyalgia.

And I think only with the appearance of this 2012 paper do I see convincing evidence that this is not only real, but it is a result of exposure to electromagnetic fields.

Q. Well, Dr. Carpenter, I'd like -- right now, I'm just trying to mark out the territory here before getting into the details.

A. I understand.

Q. It seems to me that in the disclosure that was made as to what your testimony in this case was going to be, you said that you were going to testify that Mrs. Barnett suffers from probable Alzheimer's disease, with significant memory loss and disruption of nervous system function which are either caused by or made worse as a consequence to her chronic exposure to magnetic fields as well as a variety of other symptoms caused by the stress of her exposure.

That was the testimony you intended to give in October of 2011.

A. That is correct.

Q. So, you're telling me today that since then you have decided that Mrs. Barnett does not suffer from probable Alzheimer's disease, correct?

A. Well, I haven't made that decision, but the neurologist and psychiatrist that have examined her carefully have very clearly shown that she does not suffer from Alzheimer's.

Q. Well, in your report you stated, under oath, Mrs. Barnett suffers from probable Alzheimer's disease.

A. Well, that was derived specific -- directly from her own deposition and her own statements.

Q. It was her own self-diagnosis.

A. That's correct.

Q. You assumed that that was reliable.

A. Well, I assumed that further medical examination would bear that out, and clearly it has not.

Q. So, you no longer hold the opinion that is expressed in paragraph 30 here of your disclosure.

MR. SEYMOUR: Object to the form of the question.

THE WITNESS: Well, that's only partially true. Mrs. Barnett suffers from significant memory loss and disruption of nervous system function. That -- those are characteristics of Alzheimer's disease, but they are the central characteristics of electro hypersensitivity which, at the time I prepared this, I did not feel was sufficiently well documented by the weight of the evidence of scientific reports and for which I've changed my mind.

So, I certainly no longer agree that it's probable Alzheimer's disease. And you notice I did say probable, because it was not

physician diagnosed. It clearly is not Alzheimer's disease.

BY MR. FITZGERALD:

Q. Well, Doctor, isn't it a fact that when physicians diagnose Alzheimer's disease they diagnose it as probable Alzheimer's disease unless the diagnosis is based on an autopsy?

MR. SEYMOUR: Object to the form of the question.

THE WITNESS: That used to be the case. It is no longer the case. In the era of modern imaging of the brain, Alzheimer's can be diagnosed definitively before death. It certainly used to be that you only could diagnose on the basis of histologic analysis of the brain.

BY MR. FITZGERALD:

Q. You say here, in paragraph 30, Mrs. Barnett suffers from probable Alzheimer's disease with significant memory loss. You are connecting the significant memory loss in this paragraph to her Alzheimer's disease; is that right?

A. That's correct.

Q. Yes, okay.

Now, since then you've changed your opinion and you formed another opinion.

MR. SEYMOUR: Object to the form of the question.

BY MR. FITZGERALD:

Q. Correct? You have formed an opinion concerning hypo electromagnetic sensitivity sometime in the last month, correct?

A. I have become convinced within the last month or two that electrical hypersensitivity is a real disease and that it has -- while it varies in the exact symptoms from one person to another, it is associated with memory dysfunction, a variety of neurological and actual physical symptoms.

Q. Please, Doctor, you've said that several times. As I say, I'm just trying to mark out the territory here.

You have developed an opinion specifically with respect to Mrs. Barnett concerning electromagnetic hypersensitivity?

A. That is correct.

Q. Correct? And there's nothing about that opinion in this disclosure, is there?

A. That is correct.

MR. SEYMOUR: Object to the form of the question.

THE WITNESS: The diagnosis -- I am accepting the symptoms that she reports, but the diagnosis that I had expected to use to explain those symptoms is clearly not correct, but the symptoms are real and documented by some of the exams.

And I think the rational explanation is that Mrs. Barnett suffers from electro hypersensitivity.

MR. FITZGERALD: Perhaps you can enlighten me, Mr. Seymour. How are the defendants supposed to respond to a new, completely new theory of damages undisclosed in any expert witness declaration by the current extended deadline of the 22nd or 23rd of April?

MR. SEYMOUR: That's an extraordinary statement from you, Mr. Fitzgerald, who we've -- you've had a copy of Dr. Hishaw's report that we just got a few days ago. We sent it to you on the very day we got it.

You had an opportunity back in January to participate in Dr. Hishaw's study and you turned it down. You waived any objection to the timing of this.

As soon as we got a copy of the Hishaw report we sent one to you and we sent one to Dr. Carpenter. And he then had the opportunity to look at what he said in 30, where he talks about various symptoms, and recognized that because she no longer is being exposed to your EMFs she is beginning to bounce back.

And that explanation is a hypertension. And it plainly shows that during those years, when you were bombarding her with EMFs, she had the symptoms and his statement now continues to verify that.

The question is what is the vehicle that creates those symptoms. At the time it appeared to be familiar Alzheimer's. Now, in review of Hishaw's report, which you have had and we've had discussions about as recently as two days ago, it now is suddenly a new set of facts which you have refused to recognize yourself or participate in yourself.

Back in January of this year we expressly told you that an evaluation had been requested by Dr. Sobel and wouldn't you like to share in it and help oversee it so we make sure it's done fair and square. And you turned that down.

You may not object to this witness himself doing what you should have done.

MR. FITZGERALD: Mr. Seymour, this witness is the subject of a disclosure that you filed --

MR. SEYMOUR: Correct.

MR. FITZGERALD: -- as to what he's going to say in this case. I'm entitled to depend on it.

MR. SEYMOUR: Correct.

MR. FITZGERALD: We've been entitled to depend on it in preparing our response.

After I got Dr. Hishaw's report, I asked you whether there was going to be any -- whether you wanted to change Dr. Carpenter's opinion, whether there was a point in going forward with this deposition.

MR. SEYMOUR: That isn't what you asked me about at all. You asked me about Sobel. And I told you on the phone that it looked like Hishaw was going to find there was no Alzheimer's, and that you would have an opportunity to talk to Dr. Sobel about that because it was Dr. Sobel who requested that evaluation.

MR. FITZGERALD: I need to take a break. I have to decide if I'm going forward with this deposition.

MR. SEYMOUR: Very good.

VIDEOGRAPHER: The time now is approximately 10:48. We are now going off the record.

(Recess taken.)

(Defendants' Exhibits K-1 and K-2 marked for identification.)

VIDEOGRAPHER: The time now is approximately 11:08 and we are now back on the record.

MR. FITZGERALD: For the record, I have just asked the reporter to mark as Defendants' K-1 a letter dated March 27th, 2012 that I wrote to plaintiff's counsel; and the response to that letter from the following day, March 28th, 2012, from

defendants' counsel.

That was sent electronically and does not bear a signature, but it's got the S slash and the line on it. I think there is no dispute.

MR. SEYMOUR: No. That's fine.

MR. FITZGERALD: I'm terminating this deposition.

MR. SEYMOUR: Let me make a statement.

There's absolutely no basis for your terminating the deposition itself. You can terminate your direct examination, but we will proceed with our right to cross-examination on the subjects that you have talked about.

The statements in our letter of September 28 -- I'm sorry -- March 28 continue to be absolutely true. We discovered the existence of the study that you made reference to, the J-1, yesterday afternoon while discussing these matters with Dr. Carpenter.

And as I indicated earlier, we actually went out last night to Staples, postponing supper, in order to make copies to provide them to you as quickly as we had them in our hand.

There's been absolutely no delay of any kind in keeping you informed. You were not in a position to be reached at that time. Indeed, you were an hour late coming in here even this morning. But we're -- we've done everything expeditiously, and unless you're engaged in some gamesmanship to try to misuse the Hishaw letter, we believe your position is unreasonable.

But you have a right to waive your rights. If it becomes an issue, a court can decide whether the interest of justice include going ahead and getting this witness's testimony about what the -- in his area of responsibility now appears to be the explanation for the extraordinary change in Mrs. Barnett from her neurodegenerative cognitive loss even at the time you took her deposition.

And now being away from the CL&P EMFs, her apparently bouncing back on a number of fronts, particularly what was once understood to be Alzheimer's disease, but because the symptoms, as Dr. Hishaw has discovered and as we have disclosed to you immediately, have faded, that doesn't alter other aspects of Dr. Carpenter's report.

He will talk about the likelihood of advanced chance of developing cancer, which is part of our case, and the impact of loss of 20-plus years of the woman's life during the time she was being exposed to EMFs and the other symptoms associated therewith.

You make a serious mistake, I think, in waiving your right to inquire into those things, but you should act as you're advised and we'll proceed to act as we'll advise. And we thank you.

We invite you to attend and object, if you like, to any of the questions. But now we are ready to proceed with our examination of Dr. Carpenter on cross.

Are you prepared to terminate from your point of view?

MR. FITZGERALD: First of all, let me apologize for something. I thought the deposition was at 10:00 and I was early. So, I see that I noticed it for 9:00. I don't know why I did that when I had to drive up here from Connecticut.

MR. SEYMOUR: We came up last night at some expense to our own schedule and ultimately to the client in order to accommodate you to be on time.

MR. FITZGERALD: Secondly, the reason I marked these documents is that I asked you in paragraph A of the March 27th letter to advise if you still intended to call Dr. Carpenter to testify in accordance with his witness statement of December 13th, 2011.

MR. SEYMOUR: And as at that time the answer was absolutely truthful, absolutely truthful. We saw that report for the first time last night or yesterday afternoon. You've seen it within 24 hours of our having seen it, actually probably 14 hours of our having seen it, after we went out in the cold evening to make a copy for you.

MR. FITZGERALD: Doesn't matter.

MR. SEYMOUR: It does matter.

MR. FITZGERALD: You haven't -- I'm entitled to rely on the expert disclosure, which I did. And that's what I came here to examine on.

MR. SEYMOUR: And expert disclosure is good as of the date it's written. You know that perfectly well. Time doesn't stand still. Science doesn't stand still.

Dr. Hishaw's report, which you didn't want to participate in, and it had -- that whole study has occurred since Dr. Carpenter made his report.

Are you saying that nothing since the time he made his report can be inquired into by deposition? Is that what discovery is all about, Mr. Fitzgerald?

MR. FITZGERALD: Nothing -- no new subjects can be introduced that were not -- that's exactly what discovery is about, to give the other side fair warning of what your case is.

MR. SEYMOUR: Sure, and find out if there have been any developments since that report. We will let the judge decide what's admitted or not.

MR. FITZGERALD: You do make one good point, which is that there are other things in the disclosure besides the now-retracted Alzheimer's opinion and besides the new opinion, which is not there.

And so, I really should -- I really should examine him about the testimony that is foreshadowed in the disclosure that he still intends to give. So I will do that. It won't take long. But I am not going to examine him about Alzheimer's, and I'm not going to examine him about electro hyposensitivity.

If you wanted to offer him to testify to a completely new disease that he didn't believe she had when he executed the original disclosure, you should have sought permission to change the disclosure and then I would have had something appropriate to examine him on. You have not done that.

MR. SEYMOUR: You mischaracterize, of course, his declaration entirely. He has not retracted any opinion. He has acted on what the information that was provided to him given his evaluation at that time.

He has since been given the Hishaw report, which shows that the -- simultaneously with your being given it. So, you're being informed in exactly the same moment that he is that Dr. Hishaw says there's no sign of Alzheimer's, but she still has other symptoms and has had the other symptoms, all of which are in full accord with what he concluded -- or included in his statement. And he has an obligation to bring that current, based on the new information.

A judge will decide ultimately whether that's going to be admissible or not. Don't you worry about it. Let's go ahead with the other things.

MR. FITZGERALD: I'm not going to ask Mr. -- Dr. Carpenter any questions about his diagnosis.

MR. SEYMOUR: It's not a diagnosis.

MR. FITZGERALD: Or his -- I'm not going to ask him questions --

MR. SEYMOUR: It's an opinion.

MR. FITZGERALD: An opinion?

MR. SEYMOUR: Right.

MR. FITZGERALD: Well, I am going to ask him questions about opinions, but I'm not going to ask him any questions about his opinion concerning the existence or etiology of hypo -- electro hyposensitivity in Mrs. --

MR. SEYMOUR: That's your privilege. We intend to --

MR. FITZGERALD: -- Prescott, because that was not embraced within the notice of what we should be prepared to examine.

MR. SEYMOUR: But was disclosed to you within 24 hours of our becoming aware of it.

MR. FITZGERALD: Doesn't make any difference.

MR. SEYMOUR: Any further questions?

MR. FITZGERALD: Yeah. I'm skipping -- there won't be many. I'm skipping ahead to questions that don't deal with her specifically.

BY MR. FITZGERALD:

Q. Dr. Carpenter, what is your occupation?

A. What is my occupation?

Q. Yes.

A. I'm a public health physician.

Q. And do you have a license to practice medicine?

A. No, I do not.

Q. And so you are a physician in the sense that you have an M.D. academic degree.

A. That's correct.

Q. Have you ever practiced medicine?

A. No, I have not.

Q. Have you ever treated an individual patient in any context?

A. Not other than as a medical student under supervision.

Q. Have you ever made a medical diagnosis of individual patients for purposes of prescribing treatment?

A. No, I have not, except as a student.

Q. What's the difference between a public health physician and an epidemiologist?

A. Well, they're significantly different, although a lot of what I do is epidemiology. An epidemiologist is usually someone who has obtained a PhD in epidemiology.

A public health physician is someone who practices the profession of public health, which is -- which differs from the practice of medicine in that it tries to reduce disease in the population.

It's a population-based science, rather than dealing with individuals who happen to be ill or -- but it's not a matter of treating one person at a time.

So, I think we differ quite dramatically in training. Physician's training is much broader than an epidemiologist, but an epidemiologist's training is much more in-depth in the specifics of epidemiology and statistics.

Q. In paragraph 6 of your declaration you state, "After completion of the New York State Powerlines Project I became the spokesperson for New York State on the issue of human health effects of EMFs."

Were you the spokesman for the entire state?

A. Yes. I believe that I can say that I was the -- on the issue of health effects. That is the responsibility of the State Department of Health. And I was designated by the Commissioner of Health to respond for the state on all issues related to EMF.

Q. And during that period of time did any agency of the State of New York adopt any standards or guidelines for exposure to transmission line magnetic fields?

A. Yes. The State Public Service Commission did adopt, for the first time, a standard for magnetic field at the edge of right of way.

Q. What was that?

A. It was 200 milliGauss.

Q. And is that standard still in place today?

A. Yes, it is.

Q. In that same paragraph 6 you say, "In 2009 I was invited to make a presentation to the president's cancer panel on the health hazards resulting from exposure to electromagnetic fields."

In the course of that presentation did you make the case for EMF being a health risk?

A. I did, indeed. Should you care for it, I have a copy of the publication that resulted from that presentation. The presentation was geared both to power line frequency fields and radiofrequency fields.

Q. And this was a -- you're referring to something that you published.

A. This is from the official proceedings of that meeting of the president's cancer panel in January of 2009.

Q. This will -- this document shows us what you presented to the panel.

A. That's correct.

Q. Okay. And did the president's cancer panel make any findings that EMF exposure is a cause of cancer?

A. No, they did not. In their final report they discussed the controversy, but they did not draw firm conclusions.

Q. In paragraph 6 of your declaration you refer to two books that you have co-edited. And one of them is called Biological Effects of Electromagnetic Fields. Right?

A. That is correct.

(Defendants' Exhibit L marked for identification.)

BY MR. FITZGERALD:

Q. In looking at Exhibit L, do you recognize that as a copy of the cover page from volume two of that two-volume book?

A. Yes. It is that.

Q. And a copy of chapter 15 of public health implications of magnetic field effects in biological systems, which you wrote yourself.

A. That's correct.

Q. Could we move to the last paragraph of -- I'm missing the page that I'm interested in. No. It's just out of place, page 228.

A. Yes.

Q. Read that last paragraph to yourself about the concept of prudent avoidance by Morgan.

A. Yes. I've read it.

Q. So that you wrote this in -- what year was this, 1994?

A. 1994.

Q. So, this represented your opinion in 1994?

A. That is correct.

Q. And could you just summarize briefly for us what is the doctrine of prudent avoidance by Morgan?

A. Well, the concept of prudent avoidance is basically that, in the face of so much uncertainty with some evidence of hazard, but lack of understanding of things like mechanism and good animal models, the rational thing for both governments and individuals to do is to take steps that are not terribly disruptive or terribly expensive so as to reduce exposure to electromagnetic fields.

Q. And I'm sure you recall testifying at the hearings held by the Connecticut siting council in 2007?

A. Yes.

Q. And do you recall supporting that same policy in that testimony?

A. I don't recall my statements in that testimony, but I'm sure I was supportive of that policy because I am yet today supportive of that policy.

Q. Okay. Do you know which states of the United States have adopted some form of prudent avoidance as a regulatory policy for electric transmission lines?

A. No, I don't.

Q. Okay. As applied to electric transmission lines, is it reasonable to say that the prudent avoidance concept would call for implementation of no-cost and low-cost measures for reducing fields when new facilities were built, or existing facilities were being modified, but not for wholesale reconstruction of the existing electric system?

A. Yes. That is correct.

Q. Now, in the bio initiative report -- when was that published?

A. I believe that was 2008, 2009. We have had our fifth year anniversary, and we are currently updating the bio initiative report. We're just now organizing chapter authors.

Q. Does it have a release date of 2007?

A. 2007.

Q. In the bio initiative report you called for a planning limit of one milliGauss for structures adjacent to all new or upgraded power lines that are occupied by children, and two milliGauss for other structures.

Do you recall that?

A. Well, to say that we called for that is not quite correct.

Q. Okay.

A. What we stated was that if one were to set a standard based on the weight of the evidence for human health effects from power line frequency magnetic fields, they would be of that order.

We then state that we recognize that that is an unrealistic standard at present, but that this is really an extension of the prudent avoidance concept, that since 1994 or 1986, when the power lines report came out, the evidence has only gotten stronger for harm.

And it becomes an issue of society's willingness to pay for reducing exposure that goes beyond the prudent avoidance concept, which is that you do what you can that isn't very expensive.

But those numbers were set as, yes, a recommendation from us, but not a statement that we thought that they should be established as firm regulatory guidelines in the short term.

Q. Okay. And, even as far as the suggestion went, you were not suggesting retrofitting or relocating existing power lines that produced fields higher than one or two milliGauss at that time?

A. That is correct.

Q. Now, you frequently get phone calls from people who are concerned about magnetic fields in their homes, don't you?

A. Yes, I do.

Q. And they ask you questions such as whether they should buy a particular new house or whether they should move from the house that they're occupying?

A. Yes.

Q. And what -- how do you respond?

A. Well, I usually respond by trying to put risks of development of cancer. And cancer, I think, remains the disease of greatest concern because the evidence is strongest for cancer. I try to put that in perspective with other risks.

And in terms of recommending that somebody should sell their house, I think I've only done that once in my life, which was to a physician from Potomac, Maryland, whose house was almost immediately under. It seemed to me it was closer than New York State guidelines for edge of right of way.

But a person had, I believe, four young children and had within the children's bedrooms fields of the order of 20 or 30 milliGauss.

And what I told him is if it were me I would move because of concern for the children's susceptibility to leukemia.

At the same time, I enunciated the analysis that I and Anders Ahlbohm published sometime ago, that if the risk of developing leukemia in the general population is one in 10,000 per year, and if exposure to magnetic fields of the order of two milliGauss increases that risk by a factor of two, that is two children per 10,000 would develop leukemia per year.

And therefore it isn't that every exposed person is going to develop cancer, yet there is a specific and quantifiable elevation in risk. And that any parent concerned about the health of the child has to put together a variety of concerns, of which exposure to magnetic fields is only one.

Q. Okay. In paragraph 10 of your declaration you list the cases in which you have given testimony by deposition or at trial.

A. Could I have back the copy of my statement?

Q. Sure.

A. I have a draft here.

Q. Right. Let's get the actual one. Here you go.

A. Thank you.

Q. Let me start over.

In paragraph 10 of your declaration you list the cases in which you have given testimony by deposition or at trial in the four years preceding the date of your disclosure.

A. Yes.

Q. Have you provided any testimony since that time?

A. Yes, I have. And actually, I did print out this morning the complete list of depositions and testimonies, if I can find it here. That goes earlier as well as later.

MR. SEYMOUR: Have you got a second copy of that, by chance?

THE WITNESS: No, I don't, unfortunately.

MR. FITZGERALD: Let's mark this. You can switch over now.

(Defendants' Exhibit M marked for identification.)

VIDEOGRAPHER: The time now is approximately 11:38 a.m. And now we are going to end tape one of today's deposition and we will be off the record.

(Off the record.)

VIDEOGRAPHER: The time now is approximately 11:40 and we are back on the record. And this is the start of tape two of the deposition of David O. Carpenter, M.D.

BY MR. FITZGERALD:

Q. Dr. Carpenter, you've just produced a two-page document that we marked as Defendants' Exhibit M. And as I understand it, this is a complete list of the cases in which you have given testimony by deposition or at trial since January of 2003; is that right?

A. That is correct.

Q. Well, I --

A. There are a few cases earlier than that, but I don't have good records of those.

Q. I'm not going to go all the way back to 2003. I think I will just start with what's in your disclosure and then we'll complete it with the ones that you have here in this file.

The first case appears to be Clopten et. al. against Monsanto.

Do you remember what kind of a case that was, what was involved?

A. Well, I've been very involved in litigation in Anniston, Alabama of health effects of people living near the Monsanto plant that manufactured PCBs. So almost all of these that are related to Monsanto are either Anniston or, in one case, the Salucious split off from Anniston and the issue of which company was liable for it.

Q. But in any case, PCBs?

A. PCBs.

Q. Okay. So that's true of the Paulsen case, which is the second one listed.

Now we come to one, Martinez against Entergy Corporation?

A. This is also a PCB case. These are two people that worked in a lab.

Q. That's all I need to know.

Wayne against Pharmacia Corporation?

A. PCBs.

Q. The same would be true of the next Wayne case?

A. That's correct.

Q. Passariello, I know about.

Before the Pennsylvania Public Utility Commission, testified on behalf of the Saw Creek Estates Community Association?

A. This was a power line routing case.

Q. And what was the context of your --

A. The next two --

Q. -- and you testified on behalf of some -- of a group that was opposing the power line?

A. That's correct. Opposing the routing of the power line.

Q. James Alford against the Kuhlman Corporation?

A. PCBs.

Q. Wayne against Pharmacia Corporation?

A. PCBs.

Q. Then we come to the Minnesota Public Utilities Commission.

A. Again, a power line routing case.

Q. And then Highland Lake Estates against Republic Services of Florida?

A. This was expansion of a hazardous waste site in an urban area.

Q. Okay. And then Monsanto, again, so that's PCBs?

A. Well, no. That one is primarily dioxins.

Q. Dioxins, okay.

A. That was a plant in West Virginia that manufactured Agent Orange.

Q. And then Highland Lakes Estates against Republic Services of Florida?

A. That, again, like the one above, is a hazardous waste site expansion.

Q. Okay. Williams against Jacksonville?

A. Frankly, I'm not recalling what that was. It started out as a lead exposure case.

Q. But not an EMF case?

A. Not an EMF case, no.

Q. Okay. Cybart, I know about.

Now I'm on to Defendants' Exhibit M, Snoops against Lyon Associates?

A. PCBs.

Q. Martinez against Entergy?

A. PCBs.

Q. And AHM and Mark Morrison against Portland Public Schools?

A. That's Wi-Fi.

Q. Okay. Have you ever been in a position where a party to a lawsuit offered trial testimony of yours, to be presented by you, that was excluded by the court?

A. Yes, I have, on two occasions.

Q. And what were those occasions?

A. The Alford -- let me find this again. The Alford -- no, I'm sorry, not Alford.

May I see the longer version there?

It was Adams versus Cooper Industries, again, a PCB case. That was in 2006. I believe, I believe that's the only one.

Q. And what was the ground of exclusion there, if you remember?

A. In that case I had been asked by the plaintiff's attorneys to develop a medical monitoring program. And I was excluded because I was not licensed to practice medicine in the state of Indiana, I believe it was. But it was the situation where effectively all of the plaintiff's experts were excluded.

Q. All right. Let's move, please, to paragraph 23 of your declaration. And you start off saying, "The World Health Organization rates power line magnetic fields as a possible human carcinogen." And there's a citation to IARC, which I will pronounce IARC, 2002.

Do you see that?

A. Yes.

Q. What is IARC?

A. IARC is the International Agency for Research on Cancer. It's a component of the World Health Organization, located in Leon, France. And it basically is one of the major components of WHO, focused entirely on cancer.

Q. And what is IARC's basis for listing an agent or substance as a possible human carcinogen?

A. Well, they have a formal process. They convene expert panels of people from around the world that have expertise in different areas, and usually accept the recommendations of those panels.

They've recently added radiofrequency fields as a possible human carcinogen. I know more about that decision. First of all, very recent. And the names of the individuals on the panel have been published. I'm not aware of who is on this panel.

But it's a thoughtful, deliberative decision, and they classify substances as known human carcinogens, probable human carcinogens, possible or unable to classify, or not human carcinogens. So, five categories.

Q. And how is coffee classified?

A. I believe as a possible human carcinogen.

Q. What about pickled vegetables?

A. I think it's classified as possible, but I think it probably should be probable.

Q. Has the World Health Organization sponsored a review of the science concerning potential human health effects of exposure to ELF?

A. Yes. They have had several reviews.

Q. And has it recommended adoption of any exposure standards?

A. No.

Q. Has the World Health Organization concluded that EMF exposure causes any form of cancer?

A. Well, it's obviously rated EMF as a possible human carcinogen, but it has not made more positive recommendations than that.

Q. Paragraph 23 of your affidavit still you say, "There's a large body of evidence that provides multiple mechanisms which may be the basis for the development of cancer."

Do I read that correctly as saying they may be and they may not be the basis for the development of cancer?

A. Yes. That's correct.

Q. It's true, isn't it, that there is no mechanism by which transmission line magnetic fields causes cancer that has been generally accepted or recognized by the scientific community?

MR. SEYMOUR: Object to the form of the question.

THE WITNESS: It's certainly true that there is no single mechanism that has been identified as causing cancer from electromagnetic fields, but that is also true for a majority or maybe not a majority, but about half of other carcinogens.

And the ones I mentioned particularly are dioxin and arsenic, both of which are rated as known human carcinogens, but they do not cause direct damage to DNA, as does not magnetic fields.

We have, for all three of those substances, a variety of possible mechanisms, any one of which could be the ultimate cause, but more likely all of them contribute.

And that includes induction of genes, development, stimulation of things like heat shock proteins, development of reactive oxygen species, a variety of things that could underline the carcinogenic effect.

But not having one single identified mechanism in no way invalidates the human studies that demonstrate the associations between exposure and disease.

BY MR. FITZGERALD:

Q. But actually, you see, I was asking you about what you said. All I'm trying to do here is to put limits around what you've said and not said.

In this particular paragraph you said that there are -- there is a body of evidence that provides multiple mechanisms which may be the basis for the development of cancer.

So we're just talking about mechanisms right now.

A. That statement is absolutely correct.

MR. SEYMOUR: Object to the form of the question. And please don't argue with the witness.

BY MR. FITZGERALD:

Q. And so -- I'm not arguing I don't think. I think we are agreed that what you meant to say was that it -- each of these mechanisms may or may not be a cause.

MR. SEYMOUR: That's been asked and answered.

BY MR. FITZGERALD:

Q. That's correct, isn't it, Dr. Carpenter?

A. Yes.

Q. Yes, okay. Now we can go on to paragraph 18, where you say that -- wait a minute. Well, this is still general causation, so, I guess we can stick with that. No. I don't think I will ask you about paragraph 18.

Yes, I will, it's general causation. I do want to ask you a question about the studies that you reference in paragraph 18.

What kind of a study was the Qiu et. al. study that you reference?

A. Just give me a moment to...

Q. Take your time.

A. Qiu was the study of Alzheimer's in relation to power in the frequency fields. And all I have in -- the only statement I have in my review article, without going to my office and getting that paper, is that they demonstrated an odds ratio of 2.3 that was statistically significant, indicating that those people exposed to power line fields were 2.3-fold greater risk of developing Alzheimer's than the unexposed people.

Q. Okay. I think I have a copy of the article.

A. Yes.

MR. SEYMOUR: Can we mark it, please?

BY MR. FITZGERALD:

Q. Is that it? Is that the right article?

A. That's the right article.

MR. FITZGERALD: Sure, we will mark it.

(Defendants' Exhibit N marked for identification.)

BY MR. FITZGERALD:

Q. How was the exposure of the subjects of this study estimated?

A. Well, this was an occupational study, so it's a study of older individuals, 75 and older, in Stockholm, Sweden. And they had 265 Alzheimer's patients -- I'm sorry -- 202 Alzheimer's patients.

And they were relating risk of Alzheimer's to lifetime principal job and categorizing the jobs on the basis of whether or not there was significant exposure to EMFs.

Q. And how did they express what they estimated the exposures to be?

A. Well, it's expressed as odds ratio. It's a comparison of the rates and -- supposedly exposed to the supposedly unexposed population.

Q. But how -- how did they characterize the exposure of the exposed? Was it just an on/off switch or?

A. It was just a lifetime occupational exposure, so they had -- again, I should look probably a little more detailed at the methods, but in most -- they used a job-exposure matrix.

So, they took every job and categorized whether that job would be likely to involve exposure to magnetic fields, and then they also used direct measurements for numerous occupations to, rather, to validate just the job exposure categorization.

I mean, it obviously is not as -- exposure assessment in these kinds of studies is also very difficult because you're looking at a lifetime exposure or lack thereof.

Q. Would you turn to page 693, where we find the conclusion. The last paragraph begins, "Our study provides limited evidence to the potential role of long-term occupational ELF MF exposure in the development of Alzheimer's disease and dementia in men, but not in women," right?

A. Yes.

Q. And do you have any reason to take exception to the author's characterization of the results of their study?

A. No. I think the -- that characterization is what their results suggested. You know, I'd ask why in men and not in women, when other studies have clearly shown a relationship in women.

The reality is that men are much more likely to be in occupations with high EMF exposure. And my interpretation of this is not that women are not vulnerable, but that women in this particular study did not have sufficient exposure to lead them to have statistically significant results.

Q. But if the women -- the classification went by job title, didn't it?

A. That's correct.

MR. SEYMOUR: Object to the form.

THE WITNESS: But, you know, in drawing conclusions on any relationship like this is, I think I have made clear in my statements, I do not depend on any single publication, but rather the weight of the evidence. And other studies have been specifically of women.

BY MR. FITZGERALD:

Q. But all I'm doing, Doctor, is asking you about what's in your declaration.

A. Yes. That's fair.

Q. The next study you reference is one by Huss and others, which -- wait a second.

Do you remember what kind of study that was?

A. Well, what I state there is obviously that it was people living within 50 meters of a power line that has elevated magnetic fields. I did not specifically review that manuscript for this deposition but...

Q. Do you -- I don't think I have it, either.

Do you have a -- do you have a copy with you in your file?

A. I'm sure I have a copy in my file in my office but I don't have --

Q. No, I mean here.

A. No, I do not.

Q. I won't ask you about it then.

Now we go to page 6 of your declaration, paragraph 19. You say, "There is some evidence that exposure to magnetic fields is associated with reduced memory and ability to pay attention. There are also effects on the EEG which are reported to last even after exposure. These results have been reviewed by Cook and others."

I'm handing you an article now.

Is that the Cook article referred to there?

A. Yes, it is.

MR. FITZGERALD: The reporter can mark that.

THE WITNESS: Let me say that this paragraph specifically refers to electrical hypersensitivity.

(Defendants' Exhibit O marked for identification.)

BY MR. FITZGERALD:

Q. So, the exhibit that has just been marked is a copy of the Cook document that you referred to in paragraph 19.

A. Correct.

Q. Now, you were just starting to say that paragraph 19 refers to hyper electrosensitivity?

A. That is correct.

Q. Where does it say that?

A. It doesn't say that, but the -- I think this is actually very much where I stood prior to the recent paper that we may not discuss.

But I say there's some evidence, but at the time I wrote this I did not consider that evidence to be sufficiently strong, so that I would make a strong statement that exposure to power line electromagnetic fields results in reduced memory and ability to pay attention.

Q. But this -- let's get our terms straight.

Reduced memory and ability to pay attention is not equivalent to hypo --

A. Hyper.

Q. -- hyper electromagnetic sensitivity. They are not one and the same thing, are they?

A. Well, yes. They are components of that syndrome. You know, I mean, I think what this paragraph says is, yes, I acknowledge there's a whole literature on this. I am not at this point in time convinced that it's clearly cause and effect.

Q. Now I have to ask you about the first part of the statement you just made. What you said was that reduced memory and ability to pay attention can be a component of hyper electromagnetic sensitivity.

A. Correct.

Q. Just as it can be a component of many other syndromes, right?

A. That's correct. Yes.

Q. Now, let's look at the Cook article.

First of all, does the Cook article deal with hyper electromagnetic sensitivity?

A. No. This was published in 2006.

Q. Fine.

A. And I'm not sure when the term -- I mean what's the date of the WHO paper? That's 2008 or -9. And if you go back to that paper you see that they sort of say, well, some people call this electro hypersensitivity.

So, I think there's been a sort of consolidation around the use of that term. That's relatively recent.

Q. In any event, neither the term nor any component of that syndrome, other than reduced memory and ability to pay attention, is discussed in this Cook article; is that right?

MR. SEYMOUR: Object to the form.

THE WITNESS: Well, that's absolutely correct. And what this is, it's a review of the literature up to that point. It's actually more focused on radiofrequency than ELF, but it -- I find this to be a thoughtful and accurate article.

BY MR. FITZGERALD:

Q. Okay. Good.

A. It says, you know, there's this whole body of literature. It's not overly convincing, but it should not be ignored.

Q. All right. And what -- you've already told us this is a review article, but what kind of studies does it review?

They are experiments of some kind, aren't they?

A. Well, yes. They have a large table here that lists different publications and what they found. Now, at this point in time, there is a lot of attention to looking at EEG changes.

But if you look at table five on page 623 they're looking at, you know, finger span, moving your fingers, trailmaking and

memory test, simple reaction times, long- and short-term recall, auditory discrimination tasks. So, it's a whole variety of mental-function tasks.

Q. Were any of these exposures 60 hertz, 50 hertz?

A. Well, if we look at the title it's "ELF magnetic and ELF modulated radiofrequency fields." So, a lot of those are more than just 60 hertz tests, but they are -- these megahertz frequencies are modulated at much lower frequencies.

So, I would agree that most of these are at minimum modulated radiofrequency fields.

Q. And some of these experiments produced effects such as apparent increase of pain threshold and others produced no effects; is that right?

A. That's correct. I mean, it's -- this is why at that point in time I wanted to review an article that reported the positive results, but I don't see a consistency in the findings.

And the other point here is that most of these studies didn't have good control of exposed populations versus unexposed populations, even using the same individual as their own control.

Q. Could you look at table two, which is on page 616.

A. Yes.

Q. There's the -- the first study that's referenced is called "Fuller." And it has -- the next paragram says "parameters." And the parameters are 2,000 microtesla for -- then it says, "60 minutes."

Is that -- does that mean for up to 60 minutes?

A. For less than 60 minutes.

Q. For less than 60 minutes.

So, it could be anything less than 60 minutes?

A. It's an enormous field, obviously.

Q. That's 20,000 milliGauss?

A. Yes.

Q. This is -- they were -- these are people that are being exposed.

A. That should never have been approved by a human subjects committee.

Q. Did it have to be in order for them to do this and publish it?

A. I don't recall that particular study, but it depends on whether this is a research project, where it must be approved by a human subjects committee, or if it's a clinical procedure.

This is looking at epilepsy. Clinicians are allowed to do things that researchers never would be allowed to do. And I'm almost positive that's a clinical study just on the basis of that exposure.

Because I don't believe that any IRB, no matter what the position would be on effects of EMF, would approve that as a research.

Q. Okay. Wait a minute. Maybe there is one more question on this. No.

Let's go to page 6 of your declaration. You say that -- paragraph 22 -- that you believe that long-term levels of power line magnetic fields above four milliGauss render a home unsafe and uninhabitable because such levels will increase risk of both cancer and nervous system diseases.

What exactly do you mean by "uninhabitable"?

A. Well, I mean that I consider it dangerous for people to live in a home with fields in excess of four milliGauss.

Q. Do you -- as a public health physician are you saying that those homes should be condemned?

A. I'm not saying they should be condemned, but I'm saying that living in such a home poses a significant and documented health hazard.

Q. But you just explained to us when people ask you whether they should buy a house or sell their house you do it on the basis of a four milliGauss cut point.

You don't tell them the house is uninhabitable, do you?

A. Well, I don't tell them that it's uninhabitable, but I certainly explain to them the evidence that exposure, especially of their children, to fields above four milliGauss or even less than four milliGauss poses a significant risk that their child will develop leukemia.

Q. How many -- question withdrawn.

Do you know or have an opinion as to how many houses in the United States have at least one room with an average magnetic field of four milliGauss or above?

A. I do know, but I'm not sure I can recount accurately. There is a figure that's been published on the distribution and I found it to be a relatively -- a surprisingly low number.

If I recall correctly, it was something on less than 5 percent. Now, that's from the power line in the street, not considering appliances within the home.

Q. So, it's a small percentage, but one doesn't know -- you'd have to see how many houses there are to get an absolute number, right?

A. That's correct. And if it's 5 percent, that's still a significant number of people. And the power line in the street is only one component of exposure.

So, that figure would not accurately tell you people -- the number of people at elevated risk from magnetic field exposure.

Q. Is there any body of literature with which you're familiar that examines whether there is an association between lupus and magnetic field exposures?

A. I know of no literature that would indicate there is a relationship there. There is some evidence for effects on the immune system, but the evidence in general is that the immune system is suppressed.

Lupus is an autoimmune disease where the immune system is hyperactive. So I think I would be quite willing to say there is no relationship and I would not expect to find any relationship.

Q. Do strokes cause cognitive deficits?

A. Yes.

Q. Does lupus -- is lupus associated with cognitive deficits?

A. Cognitive deficits are not a major component of lupus, but lupus is a disease that affects blood vessels. Lupus primarily affects the skin, the kidneys, but lupus could conceivably affect cerebral arteries as well as peripheral ones.

Q. Is attention deficit disorder associated with cognitive deficits?

A. Yes. Not always. In about 50 percent of kids with ADHD they do have cognitive deficits.

Q. How about adults?

A. Less information on adults. Only about 40 percent of children with ADHD will show symptoms as an adult. It's an area of my recent research.

Q. Let me go back to paragraph 30 of your declaration. The last clause in that paragraph is, "as well as a variety of other symptoms caused by the stress of her exposure."

Now, what do you mean by the stress of her exposure?

A. Well, the one thing that comes through so strongly from her deposition -- again, I don't have a printed-out copy of the full thing -- was she was absolutely convinced she was being poisoned by the magnetic fields in her home.

And that anxiety and fear of developing disease is what I was talking about. Stress for whatever cause, whether justified or not, is well-known to cause a host of physiologic changes that lead to real disease.

Q. Now, do you know anything about the other sources of stress in Mrs. Barnett's life?

A. I only know what was in her deposition and what she stated, that she was constantly fearful for herself, for her husband, for her dogs.

Q. Actually, you only know what's in the excerpts from the deposition that Mr. Seymour provided to you.

Isn't that right?

MR. SEYMOUR: Object to the form of the question. He testified earlier that he had read --

MR. FITZGERALD: Object to the form of the question. You objected. Fine.

MR. SEYMOUR: But don't misstate his earlier testimony, please.

THE WITNESS: I did review the deposition. I had an electronic copy, which I probably should have printed out for you. But I did review that deposition, briefly glanced through it.

BY MR. FITZGERALD:

Q. And what did you learn from that deposition about sources of stress in Mrs. Barnett's life other than concern about magnetic fields?

A. Well, I think what I learned primarily is that this woman felt that her whole physical and social life was deteriorating, that her intellectual ability was deteriorating, that her husband was ill, that her dogs were dying. And it was a combination of things that were just enveloping her. She was clearly stressed.

Q. And I asked you whether you learned from her deposition about any sources of stress other than the exposure. You just mentioned two. You said her husband was ill and her dogs were dying. Anything else?

A. I don't recall other things. It was clear that she was fixated on the power lines.

Q. Have you reviewed any reports of neuropsychiatric evaluations of -- sorry. Question withdrawn.

Have you reviewed any reports of neuropsychologists concerning their examination and interviews of Mrs. Barnett?

A. Yes. I have reviewed the reports of the various physicians she saw early on, and obviously the report we've already talked about of the psychiatrist that was done this year.

Q. That was Dr. Hishaw, right?

A. Yes.

Q. So, you reviewed the declaration and records of Dr. Hasbani?

A. Yes. No. Reviewed, I skimmed them. I certainly didn't go into them in great detail.

Q. You reviewed the -- you skimmed the declaration and records of Dr. Epstein?

A. Yes.

Q. And did you learn anything from those documents about sources of stress in Mrs. Barnett's life?

A. No. I don't think I learned anything. It confirmed the impression I had from her deposition that this women was stressed.

Q. Well, did you see anything in -- what did you -- what evidence of stress related to magnetic field exposure did you find in those records?

A. I don't know that I -- well, it was clear from all of them, even people that were their orthopods, that this was an anxious woman.

Now, the source of her anxiety, most of these people did not comment on specifically except to acknowledge that she blamed everything on the magnetic fields.

But -- and I wasn't particularly interested in other aspects of her stress because, in her mind, all the problems in her life came from the power lines.

MR. FITZGERALD: Okay. That's all that I have.

MR. SEYMOUR: All right. You finished?

MR. FITZGERALD: I'm finished.

MR. SEYMOUR: Why don't we take a lunch break. It's now coming up on 12:30. And let's resume reasonably shortly, say, 45 minutes, since we don't have to go out.

VIDEOGRAPHER: The time now is approximately 12:27 and we're going to close the deposition at this point. And this will mark the end of tape two of today's deposition.

We are now off the record.

(Lunch recess.)

VIDEOGRAPHER: The time now is approximately 1:15, and we are back on the record. And this is the beginning of tape three of today's deposition.

EXAMINATION

BY MR. SEYMOUR:

Q. Dr. Carpenter, you understand you are still under oath?

A. I do, indeed.

MR. SEYMOUR: You gave some testimony earlier about the presentation you made to the president's cancer panel in 2009. I'd like to ask that publication of your presentation be marked as Plaintiff's Exhibit 1 for identification.

(Plaintiff's Exhibit 1 marked for identification.)

MR. SEYMOUR: You've also provided a copy of the paper you wrote with Ms. Sage that was published in the Review on Environmental Health in 2008. I'd like to ask that that be marked as Plaintiff's Exhibit 2 for identification.

(Plaintiff's Exhibit 2 marked for identification.)

BY MR. SEYMOUR:

Q. Can you summarize for us the essence of your recommendations to the president's panel in your presentation with respect to electromagnetic fields in particular.

A. The presentation dealt with both power line frequency and radiofrequency. With regard to power line frequency, this is material that's covered in both of those publications, but the cancer panel report is more succinct.

I conclude that the evidence is very strong that exposure to magnetic fields results in elevated risk of childhood leukemia, that there is significant and consistent evidence for leukemia also in adults. It's not quite as strong as it is for children.

I reference the one study I'm aware of where in adults both residential and occupational exposure to magnetic fields were investigated, and where the risk appears to be additive, which is what one would expect. It's really the magnetic fields that cause the disease.

I touch very briefly on other health effects, especially the relationship with neurodegenerative diseases, where I see the relationship between Alzheimer's and amyotrophic lateral sclerosis to also be strong, and mention that there are other health effects, but that these two are the most convincingly documented.

Q. And the paper you did with Cindy Sage that we marked as Plaintiff's Exhibit 2, does that also address the same set of issues?

A. Yes. It addresses exactly the same issues. This is basically a slight revision of the chapter 17 of the bio initiative report. The bio initiative report is a web-based report. It's not peer reviewed. And we in science attribute particular value to having a peer-reviewed publication. So, this was written to go into a peer-reviewed journal.

Q. So that Plaintiff's Exhibit 2 for identification is, in fact, a peer-reviewed version of the material that's in the bio initiative report?

A. It's the same material. It is peer reviewed. It's the same material, but it's organized a little bit differently to meet the requirements of the journal.

Q. I believe you used the phrase that the risk appears to be "additive" when you were describing the president's panel report.

Could you explain that a little further?

A. Well, there is another manuscript that -- it's easiest to describe that on the basis of the -- this other paper, which we have made copies of it. I don't seem to find.

Q. Do you remember the topics of it?

A. It's one of the ones you made copies of.

Q. And that we have marked?

A. Yes. No. I have it here. It's the Fetchning et. al paper, entitled "Occupational and residential magnetic field exposure and leukemia in central nervous system tumors."

Q. Yes. That's what I previously marked as Defendants' Exhibit J-4.

Could you explain to us what the significance of that study is?

A. There have been numerous studies of occupational exposure, and they all have some limitations because they are primarily based on job title rather than on direct measurement to magnetic fields. But they do show a consistent elevation in adult leukemia.

There have been very few studies of residential exposure and adult leukemia. There was one, as part of our New York State Powerlines Project, which did not show statistically significant elevations and risks. They were elevated but not statistically significant.

This is important because our consideration in this case is of an adult. And what this study shows is that if you only considered the magnetic fields in the residence of these individuals, they showed an elevated risk but not a statistically significant one.

And in this particular study if you considered only the occupation, they also showed it a little higher elevated risk but not statistically significant. But when you considered residential and occupational exposure then they found a statistically significant elevated risk of, I believe, 3.7, an odds ratio of 3.7, highly statistically significant, which is consistent with the conclusion that I've drawn, that what is important is your magnetic field exposure from all sources, and even though most studies consider only one source.

And the important conclusion from that is that almost every study is underestimating true risk from exposure to magnetic fields because of these difficulties in accurately assessing exposure.

Q. So, if they accurately presented the exposure the risk would be elevated from what is actually included in the study?

A. That's correct. Because we are all exposed, not just in our residence from the power lines, we're exposed from appliances, we're exposed when we go to work, we're exposed when we walk the streets, when we go to recreational facilities.

And nobody has been able to follow that exposure for long periods of time. People have developed meters so you can walk around and get daily levels, but what's important is many years of exposure in creating risk of disease.

Q. And in Mrs. Barnett's case, in this case, do you have any judgment as to what was the principal source of exposure for her?

A. Well, if I recall correctly, she lived in this house in Connecticut for about 20 years. The magnetic fields in the house were -- although they weren't measured at all that period of time, but from the time the power line was upgraded one can assume that they were elevated as they were in the period where they made measurements.

Early in that period she was more active. She was outside of the home more. And then, as she became more disabled, she moved her occupation into the home, and even that dwindled, according to her deposition.

So that near the end of the period that she lived there she was in the home most of the time, and certainly at night.

So, in her case, when she was spending almost all of her days and nights at home, that would be the exposure she was subjected to. Earlier on, when she was going out more, there would be varying exposures depending on where she was.

Q. You were asked during your direct examination about the studies of women as opposed to men. And in connection with Defendants' Exhibit N -- we've got a copy of it here somewhere.

Would you look at that exhibit again, please. And let me direct your attention to the next to last paragraph of the text, which appears on page 693.

A. Yes.

Q. And you'll see a sentence that reads, "We were not able to control for the possible confounding of the residential exposure that may equal the magnitude of certain occupational exposures in some cases."

Can you relate that to the issue of determining the risk for women as opposed to men?

A. Well, I think traditionally women spend more time within the home than do men. Even working women tend to have greater responsibility for maintaining the household. Whether that's justified or not is a different issue.

But I think it would be fair to assume that proportionately women would have a greater time within the home than men. And that may well be a major confounding factor as an explanation of why women did not show statistically significant relations in this particular study.

There have been other studies, however, specifically of women. One of the first studies -- I don't recall the publication, but one of the first studies was of women operating sewing machines in California, electric sewing machines where they sit close to them all day.

And one of the -- nobody expected to find a relation with Alzheimer's disease, but the seamstresses developed very high levels of Alzheimer's and became one of the first reports of this relationship.

Q. Is that a study directed by Dr. Eugene Sobel, by any chance?

A. I think it may well be, but I don't know for certain.

Q. And with respect to Defendants' Exhibit N that we were just looking at, if you dealt with a woman under the conditions of Mrs. Barnett, who spent most of her day, working day, once she became -- had a home office, as well as a mother of two very small children, would you expect to find that she was equal to the men in terms of risk from exposure to magnetic and radiofrequency fields?

MR. FITZGERALD: Radiofrequency fields?

MR. SEYMOUR: Withdraw that part. Magnetic.

MR. FITZGERALD: Objection withdrawn.

MR. SEYMOUR: Withdrawn.

THE WITNESS: I'm not sure that one can say specifically because in different occupations there are obviously very different levels of exposure.

But for the average occupational exposure, I would think that the fields measured in her home are certainly equivalent to that average exposure.

BY MR. SEYMOUR:

Q. All right. Now, you were asked also about the advice you gave to the doctor who lived in Bethesda, I think?

A. Potomac.

Q. Potomac. And you based that advice on the age of his children.

Are you aware of the age of Mrs. Barnett's children in 1990 when that very first reading was done on the high level EMF levels inside the home in Trumbull?

A. I don't recall the age of her children.

Q. I think, unless I'm mistaken, it was five or six years old.

Would that be in the bracket of concern for potential leukemia either immediately or after a period of latency?

A. Yes, it certainly would. In general, the younger the child, including in utero, the more vulnerable they are. But, you know, I should perhaps expand a little bit.

I very rarely will tell someone --

Q. I wasn't talking about the advice you gave, but the concern you felt.

A. The concern was because of the age of the children.

Q. And is there any way to predict the period of latency for those children somewhere along the line developing cancer?

A. Well, we know a fair bit about latency for leukemia from ionizing radiation, and that mostly comes from Hiroshima and Nagasaki. Leukemia has a shorter latency between exposure and development of cancer than most other cancers do. It peaks at about five years after exposure.

Now, of course, this is not a one shot in time exposure. This is a continuous exposure for as long as one is in the home. But childhood leukemia is something that occurs sort of up to the age of 20, and you would expect that there would be a latency of probably at least five years.

Q. Now, let's talk about potential for cancer generally. In your opinion, is Mrs. Barnett still subject to the potential of earlier cancer than other members of the community?

A. Absolutely. As I said, the latency for leukemia from a long-term constant exposure is probably at least five years. And if I recall correctly, Mrs. Barnett moved --

Q. In 2009.

A. 2009. So, she is -- the peak is at five years, and then it tails off up to 20 years. So, for the rest of her life she is going to be

at elevated risk of developing leukemia.

Q. Does that apply to all forms of cancer or merely leukemia?

A. Well, I would hesitate to say that the evidence is very strong for all forms of cancer. It's strongest for leukemia, first childhood and then adult. It's strong for lymphoma. There is some evidence for breast cancer, but it is much weaker.

And the evidence for other forms of cancer -- did I mention brain cancer? Brain cancer is certainly as strong as lymphoma from power line fields, not just from cell phones and radiofrequency fields.

So those are the cancers of major concern.

Now, there are isolated reports of elevations in other cancers. Again, I look at the weight of the evidence. And I do not think the weight of the evidence is sufficiently strong for me to make a more likely than not claim for the other kinds of cancer.

Q. Would it be reasonable for Mrs. Barnett to have concerns about delayed onset of leukemia, and the other forms of cancer that you mentioned, for her twin children who essentially lived through their childhood and teenhood in the same house with their mother?

A. Absolutely.

Q. So that her -- one of the sources of her stress legitimately is worrying about the children?

A. Absolutely.

Q. You were asked about your -- the book you published, and that was marked as, I think, Defendants' Exhibit L for identification. That -- if I understand correctly, that book was published in 1994.

Have the -- has the evidence developed through continuing studies added to the risk factors for EMF -- from EMF since the time you published that book?

A. Yes, it has. I think the evidence -- I wouldn't say that the risk has grown larger, but I think the evidence for an elevated risk has gotten much stronger. And that's best reflected in the meta analyses of the childhood leukemia data that I referenced in my report.

Q. You were asked some questions about standards, official standards for edge of right of way, as I recall.

A. Yes.

Q. Can you describe to us, based on your own observation and experience, what role the power industry has played in setting those standards?

A. I don't really have a lot of personal experience --

Q. Okay.

A. -- with regard to influence by power industry. I can certainly recount the basis of the standard that was imposed in New York after our New York State Powerlines Project, that standard being 200 milliGauss, when our health studies suggested elevated cancer at two milliGauss, so, two orders of magnitude off.

The Public Service Commission, at that point in time, decided they did not want to authorize any power lines that would be worse than existing high voltage power lines. So they went around to measure the magnetic field at the edge of the right of way, which was at that point determined by the electric field, not the magnetic field, and they found that the highest magnetic field was 200 milliGauss. So that was established as a standard so nothing would be worse.

Q. And it was based on the public policy of not wanting to impose a higher cost on the industry as opposed to the standard focusing just on human health consequences.

A. That's correct.

Q. Do you have a view as to whether the 200 milliGauss at the edge of the right of way would be an appropriate standard if you could write the standard yourself?

A. No. I don't think it's an appropriate standard, and that is discussed extensively actually in the review paper that you've just marked. Also in the bio initiative report. 200 milliGauss is not based on health effect studies.

Now, I would acknowledge that this is a controversial area, that we've talked about what is the magnitude of the risk if there's a doubling of the rates of childhood leukemia.

And if one were to impose the standard that would be health protective, which I think would be about two milliGauss -- one could argue between two and four, but two milliGauss would be the standard that I think would protect people, it would be enormously disruptive and enormously expensive.

So, I limit my own advice to what would be a health-based standard, recognizing that there are many other considerations that, of course, enter into our regulatory agency establishes rigorous standards.

Q. You were asked also during your direct about the significance of the absence of a mechanism, identification of a mechanism for the health consequences from EMS.

Does that prevent setting policy considerations for the need to protect human health?

A. It should not at all. And, in many regards, I think that's simply an excuse from reflecting pressures brought on regulatory bodies.

As I stated earlier, there are many chemicals identified as known human carcinogens for which there are no known mechanisms. What one should be concerned about is what is the strength of the evidence in a human population.

And you're trying to -- the goal should be to protect people from cancer or from whatever disease, whether or not you know the mechanism.

In my judgment, the evidence for there being an association between exposure to magnetic fields and human cancer is very strong. The risk is, in the greater scheme of things, probably best characterized as being modest.

But it's real, it's significant, and the fact that we don't have a single mechanism, to my mind, should make no difference at all.

Q. Now, I'd like to take a look at Defendants' Exhibit -- bear with me a second -- E. This is the excerpt from a -- I think it's paragraphs 38 and 39 and 40 of the amended complaint in this case, which identifies the various claims for diseases and injury and pain suffered by the plaintiff.

And I'd like to go down the list of items listed there, and particularly those in paragraph 40, starting on page 2 of this excerpt, and ask you to identify any of those reported or diagnosed conditions that have affected Mrs. Barnett, and identify those which reasonably are more likely than not to be associated with the emissions, EMF emissions to which she was exposed for some 20 years at the house in Trumbull, Connecticut.

Are you with me?

A. Yes.

Q. All right. Let's take a look at the quality-of-life conditions. Refers to headaches, sleep disruption, pain, uncontrolled vomiting.

Could you --

A. Well, I think all four of those are components of what is known as the electro hypersensitivity syndrome. Particularly impressive is this recent paper by McClarey, studied in a woman physician who is electrosensitive, where her primary symptom was headaches.

And although she could not detect whether the fields were on or off, by repeatedly asking her she was found to experience headaches when the fields were on.

Sleep disruption, there's a whole series of papers on sleep disruption that certainly characterize -- it's a characteristic of EHS syndrome.

Pain is a characteristic, especially bone and joint pain. And vomiting -- nausea and vomiting are also common symptoms of people suffering from EHS.

Q. The study you were just referring to is the one that was marked as Defendants' Exhibit J-1; is that correct?

A. That's correct. Yes.

Q. Now, going on down that list, could you pick out any other symptoms that are reflective of possible involvement of the hypertension or some other cause?

Have I got it wrong? Hypersensitivity, I'm sorry.

A. I study hypertension as well.

Well, I think the loss of pastimes and pleasures are likely a consequence of these neurologic symptoms of headache and sleep disruption and so forth. Nervous system disruption is -- almost means the same thing. As I stated earlier, I think there is no relationship between lupus and exposure to magnetic fields.

I know of no evidence that slowness to heal is related to magnetic fields. Balance problems, on the other hand, is -- this is a symptom reported in some people, not all people, with EHS.

Cervical nerve problems, in her case because she was in an automobile accident, I would be unlikely to attribute that specifically to magnetic field exposure, although some individuals do suffer from cervical nerve problems. And in her case, I think there may be another explanation for that complaint.

Time spent in medical consultations and tests is clearly a result of the symptoms we've discussed above. The abrupt weight loss, anxiety often causes either weight loss or rapid weight gain because of effects on appetite.

Death of family pets --

Q. I'm going to ask you to hold that one because I want to come back to it with a more specific question, but let's keep on going down the list.

Under the heading "anxiety and emotional distress," could you review that list?

A. Well, these are -- many of these are also clearly parts of the EHS syndrome. Emotional distress is when you feel like your memory function is not going well, when you can't sleep at night, and so you become anxious. That's anguish.

The loss of peace of mind, the worry about health decline, worry about professional decline, clearly this was a woman who had been an active and productive professional and not only saw loss of friends, saw loss of clients, that led to worry of loss of earning capacity and earning function.

Anxiety about effects on family, she had young children. We haven't mentioned it, but her husband developed brain cancer, which is one of the cancers specifically associated with exposure to EMF.

Q. You mean brain tumor.

A. Brain tumor. Well, most brain tumors are not cancers in the true sense of the word, but they grow inside the skull so they have very dangerous effects.

Fear about increasing health issues, again, appropriate concern. That's health issues of children, husband, and pets.

Concern over qualifying for disability, obtaining disability, keeping disability coverage. And then loss of family pets.

All of those are issues that are appropriate for someone who becomes progressively emotionally and neurologically disabled.

Q. If I could get you to turn the page. The list goes on.

A. Yes, memory loss. Now, in Alzheimer's disease memory loss is permanent. In EHS most of the evidence indicates that it's reversible. As a matter of fact, some EHS subjects report they go to work they can't think, they come home and their cognition is great.

Loss of brain functions, in Alzheimer's it's permanent. In EHS it's not. Deterioration of skills, loss of professional abilities, loss of management and organizational skills, loss of financial analysis ability, loss of money management function, again, these are all correlated with someone who is not functioning well.

It isn't that her intelligence has changed so much as her brain function has been disrupted because of the effects of exposure to magnetic fields.

Q. And how about the personality changes?

A. Loss of empathy, it's fairly difficult to feel sorry for other people when you're feeling very sorry for yourself.

Loss of focus, characteristic of EHS. When you lose empathy and lose focus that certainly has adverse effects on family relations. Alienation and loss of clients we have basically already mentioned because if you become self-centered and anxious and concerned and not sociable, people don't want to be around you.

Q. Before going on to the abnormal cell growth list, I want go back and just touch on the loss of pets, and particularly her description of the emotional impact of the loss of I think six dogs, pet dogs while they were living in Trumbull -- three pet dogs while they were living in Trumbull.

And I'd like to ask you to look at Defendants' Exhibit J-5 for identification, and ask you if you are familiar with that, and would describe what it is?

A. Yes, I am familiar with this. This is a paper done in Denver, Colorado, where we did our childhood leukemia studies. And this is a study of lymphoma in dogs based on the wire code configuration in homes.

The wire code was the surrogate measure of magnetic field exposure that was originally used by Wertheimer and Leeper in 1979 in their -- in what was really the first report of leukemia of cancer in children in relation to magnetic field exposure.

In this study they find a striking elevation in risk of lymphoma in dogs. Dogs don't get leukemia. They get lymphoma. And find significant elevations in risk, significant odds ratios.

Dogs that lived in high, very high current homes had odds ratio of 6.8, even higher than we ever saw with children. The issue about dogs is that most dogs are going to be staying at home most of the time. They may be taken for a run every now and then. So it may be 23/7 rather than 24/7, but they are good indicators of what people in a home would be exposed.

Now, the fields in Mrs. Barnett's home had very highly elevated magnetic fields. This paper would be consistent with the conclusion that the dogs were at elevated risk for lymphoma.

None of the evidence that I saw identified what form of cancer the dogs had. I think one of them did not -- was not reported to have cancer, but I would strongly suspect that the dog had lymphoma.

Q. I believe you've several times used the phrase significant "odds ratios."

Can you explain what that means?

A. Yes. An odds ratio is how an epidemiologist would explain the relationship between two populations of people or dogs or whatever, one population that you assume to be exposed to whatever your factor of interest is, the other population that you assume to be unexposed or at least less exposed.

And you then measure the frequency of disease in each of those populations, and you look at the ratio of the incidence of disease and exposed over your control. Now, that would give you an odds ratio. If there is no difference in your two populations, that ratio will be 1.0.

If being exposed to magnetic fields protects you from cancer, that relation will be one, less than one. If the risk is increased, it will be more than one. Now, statistical significance in human studies you can never absolutely prove causation. It's just not possible.

What you depend on are demonstration of associations, and you want to see associations in different studies done at different places. And traditionally epidemiologists consider results to be significant if the upper and lower bounds of 95 percent confidence limits does not overlap with 1.0.

So, when you have -- in this case, you have examples of both significant and non-significant --

Q. This case being?

A. In the REEF report. We were talking about lymphoma.

So, when exposure was characterized into two levels, high and very high, as compared to low and very low, the risk was evaluated with an odds ration of 1.6, but the 95 percent confidence limit was 0.9 to 2.2.

That would be considered an elevated, but not significantly elevated, odds ratio because the lower bound in the 95 percent confidence limit was less than 1.0.

And, on the other hand, dogs that lived in homes of very high current codes had the observation of 6.8 with the 95 percent confidence limit of 1.6 to 28.5. That is a positive and significant odds ratio.

Now, of course, one would like to see multiple studies that show these elevated odds radios that are significant, but this is the only study that I'm aware of that was done on dogs.

Q. One other technical phrase that you've used a couple of times. You refer to some of these studies being "peer reviewed."

What does that mean in practical terms? Who is a peer, and how do they review?

A. Well, most scientific journals will not publish a paper without being peer reviewed. When I submit a manuscript to a

journal, what the journal does is send it to several people, usually three, sometimes five, people that are knowledgeable in the area.

It is usually done anonymously, but increasingly one's being asked if you would agree to let your name be given to the author. But these people are often people you have never met or have had no particular relationship with, but they are still within your field, so often you are aware of their publications.

They read your manuscript. They advise the journal on whether it's worth publishing. And almost always they'll say this is only worth publishing if the author does this and that and this and that, or they may say, this is nonsense and it should be rejected.

So, it isn't perfect because it depends on who is selected as the peer reviewer, but it is -- it prevents people from publishing things that are -- where conclusions are drawn that are not justified. The goal is at least to have it prevent publication of those things. So it's a quality control mechanism.

Q. And was the dog study peer reviewed?

A. Yes, it was. It was in the American Journal of Epidemiology, which is a very rigorous journal.

Q. Now, I wanted to go back to the portions of the list from the paragraph 40 of the complaint under the heading "abnormal cell growth."

And by way of leading up to that, I'd like to show you an excerpt from what's called the RAPID study. It's been previously marked as Defendants' Exhibit J-8.

Are you familiar with the RAPID study?

A. Yes, I am.

Q. And are you able to interpret for us the significance of that particular schedule?

A. Well, the -- what this table from the RAPID study shows is some animal studies or cellular studies where magnetic exposure demonstrated clearly positive effects.

Q. Meaning they were --

A. They were statistically significant.

Q. Okay. These are good studies in terms of their reliability and quality.

A. Well, you know, you can have a negative study that's a good study.

Q. I didn't mean the outcome. I meant the quality.

A. These were studies that the review committee for the RAPID program felt they were good, and they demonstrated some positive effect of magnetic field exposure.

Q. Now, tell us a little bit about the RAPID study. If I understand it, it was authorized by Congress and some money was appropriated.

Can you tell us just what the mission was and how it functioned?

A. Well, the RAPID study was done by the National Institute of Environmental Health Sciences. It followed a series of events, started with this paper by Wertheimer and Leeper that I mentioned.

The Department of Energy funded a fair bit of research on electromagnetic fields, most of which was not a very high quality. Then our New York State Powerlines Project came along between 1982 and 1987.

And for the pittance of money we had, I think we raised the bar significantly, both on how a study should be done, by looking for conflicts of interest, by having very good dosimetry, by asking questions with clear hypotheses that were tested.

When our Powerlines Project ended, the DLE program had been to some degree discredited, and there were major questions in the minds of everybody, including Congress. And so they basically instructed the National Institutes of Environmental Health Sciences to do an expanded study.

I must say at the time I thought the design was unwise because they focused on animal and cell studies. They did no human health studies, although there had been a number of human health studies that followed the Powerlines Project, not funded primarily by U.S. agencies.

And I should say in our New York State Powerlines Project we funded 14 projects. Only two of them were human health. And in almost all of the cellular and animal studies we found effects that they could hardly be translated as to being hazards. And the RAPID study was exclusively cellular and animal studies.

Q. Two of the names that are on that page were identified as reliable studies include Martin Blank.

Can you tell us who he is?

A. Martin Blank is a cellular biologist at Columbia. He's worked on electromagnetic fields for many, many years. He's a very distinguished person.

He and his colleague, Reba Goldman, have particularly focused on gene induction from exposure to magnetic fields and with particular attention to heat-shock protein induction. Heat-shock protein is a protein that's induced in many, many cells after some sort of injury.

So, it isn't a very specific marker, but it indicates that the cells have been stressed in some way. And I believe this is -- in this case it was magnetic fields on Sancom oxidase, and that he was studying and he found that -- that this also was a marker for cellular stress, and it increased with exposure to magnetic fields.

Q. Is Dr. Blank one of your fellow authors of the bio initiative?

A. That's correct. He's an author of one of the chapters.

Q. And in your general knowledge of people working in the research field, has he got a good reputation?

A. He has an excellent reputation, yes.

Q. And are you aware that he is one of the plaintiff's experts designated in this case?

A. Yes, I am.

Q. Now, tell us about Aaron.

A. Well, Aaron is an investigator that's done a lot of work with bone. And I should say that he's by no means the first because there's -- one of the longest chapters in the books that I edited -- blocking on his name now -- but there was a very distinguished scientist -- sorry, totally blocking on his name -- that has for many years -- did for many years, he is deceased now, but studied the effects of electromagnetic fields on both growth and development.

And his work led to the clinical application of applied electromagnetic fields under circumstances where there had been

fractures of bones that were not healing properly, and --

Q. Was that Dr. Becker, by any chance?

A. No, it is not Dr. Becker.

Q. Sorry.

A. It will come to me after I stop looking.

But Dr. Aaron is at Brown University in the department of orthopedics. And he has really continued the work that had been going on and trying to understand how applied electromagnetic fields would stimulate growth of osteocytes, the cells that make bone; and chondrocytes, the cells that make cartilage.

Q. And he was the person in charge of the research project that the RAPID review committee identified as a reliable study?

A. Yes. This was a project that was testing the hypothesis of magnetic fields produced alterations in the endochondral ossification, that being the deposition of calcium into these chondrocytes.

Q. And we've previously marked as Defendants' Exhibits J-6 and J-7 studies by Dr. Aaron with colleagues, and I wonder if you could just identify those for us.

A. Yes. One is a paper by Aaron, Wang, and Ciombor, showing that applied EMFs help regulates a tumor growth factor beta one, and presents evidence that that's involved in skeletal repair and tissue engineering.

The other paper with Dr. Ciombor as the first author is entitled "low frequency EMF regulates chondrocyte differentiation and expression of matrix proteins."

Q. Now, looking at -- back at the list of conditions that Mrs. Barnett experienced that's in Defendants' Exhibit E, the excerpt from the amended complaint, that very last group of -- under the heading "abnormal cell growth" begins with some reference to effects on bone, bone tumor, hip resectioning, bone hotspots.

Is it a reasonable conclusion, or at least concern on her part, that the EMFs had a role in causing those conditions in her?

A. It's reasonable for concern. I would not go so far as to say that it's more likely than not that the bone hotspots and the bone tumor were caused by her EMF exposure, but there is enough evidence for the effects of EMF on bone to justify her concern.

The hip resectioning is a consequence of the tumor, obviously. So, you know, there is very strong evidence that EMF influences bone growth, but whether it is actually responsible for triggering tumors, whether it stimulates both growth in one area more than another, I could not say has been well documented.

Q. If you would look at the other items on the list, ovarian cysts, other cysts, nodular density, spinal lesion, abnormal mammogram, are any of those significant in connection with the possible effects from electromagnetic fields, in particular as they may relate to the development of cancer?

A. I think there's no evidence for an association with cysts. The spinal lesion, that's not very specific. If this is a bone spine, then it falls into the bone category above.

It normally would mean to me a nervous system lesion, which I would doubt would be associated with EMF. The abnormal mammogram, there is some evidence for a relationship between breast cancer and exposure to EMFs. Interestingly, it's strongest in men, but there is also a building body of evidence in women.

An abnormal mammogram is certainly reflective of an early stage of the development of breast cancer. So, that's a

possibility.

Q. Bear with me a second.

Could any of the conditions that we've identified on this list represent initiating events for future health problems?

A. Well, certainly the abnormal mammogram is something that would be exactly that. Now, the -- you know, prior to the clear statement by a neurologist/psychiatrist that she does not suffer from Alzheimer's disease, many of these symptoms are characteristic of early Alzheimer's. And that is basically why I -- I basically swallowed the idea that she had early Alzheimer's on her self-report.

I know a fair bit about Alzheimer's. My mother died of Alzheimer's. And sleep disturbances, headaches, unusual behavior, or anti-social behavior are very characteristic.

But I think, as I said earlier, there is another explanation for that in someone that, at this point at least, does not appear to have Alzheimer's.

Q. And let me just be sure that we're all talking about the same thing on Dr. Hishaw's neurological report. He's connected with Arizona State University, I believe, their medical center. I will find the letterhead here. Just a minute.

It's Exhibit G, Defendants' Exhibit G. This is not the marked copy, which is somewhere in the pile of papers here, but that's another photocopy of the report. We sent you a copy of that report when it was received.

A. That is correct.

Q. And this report said what to you in terms of the symptoms and conditions that Mrs. Barnett was suffering?

A. This report makes it very clear that Mrs. Barnett does not have Alzheimer's disease. Not only does she perform well on cognitive function tests, the laboratory test, the apolipoprotein E, which is elevated in people with Alzheimer's, and the presenilin one are both negative.

So, her symptoms cannot be explained by, at least, mature Alzheimer's.

Q. On the other hand, you came to a conclusion that the symptoms could be explained by EHS.

A. That's correct. They could also be explained by Alzheimer's, also, but she doesn't have Alzheimer's. But they certainly fit the profile of what EHS has been characterized to be.

And on the basis of the new publication, where you have a blinded clinical study in a neurology department by competent physicians, I consider that to be proof that the disease is real and that it's caused by EMF exposure.

Q. She moved from Trumbull, Connecticut, the house next to the power line, in I think it was August 2009, down to a house with -- I think it was something like a .5 milliGauss reading in it.

Does getting away from the EMFs play any part in the nature of her symptoms and the lasting nature of the symptoms and which ones might go away and which ones would still linger?

A. Well, there's not really --

MR. FITZGERALD: Objection to form. I just find that incomprehensible.

If you understand it, you can answer it.

BY MR. SEYMOUR:

Q. All right. Well, let me try it in a simpler fashion.

To what extent does EHS relate to continuing exposure of high level EMFs and getting away from that exposure, if you can answer that?

A. I can answer that.

While there has been inadequate careful study, all of the anecdotal information from EHS sufferers is that when they get removed from the field most of the symptoms are reversible.

We have people living on mountaintops without electricity to get away from exposure to these fields. And they find when they go back into an urban setting that they have symptoms again.

So, I would not find it -- I do not find it at all surprising that in a new surrounding, where she's living in a home with lower magnetic fields, that her symptoms have reduced. Apparently they haven't totally gone away, but they've been drastically reduced.

Q. So, assuming the EHS is the correct explanation, what we have here is a person who, while she was living in the setting with these high levels of EMFs, was being subjected to these and experiencing these wide range of symptoms, but as she got away from it and escaped from the high EMFs then they began to recede.

A. That's correct.

Q. Now, can we take a look at J-1, which is the most recent -- or the very recent study you referred to about -- on ENS -- EHS.

A. I have one.

Q. Now, I wonder if you could really take us through the blind study and what it showed and what the -- maybe preliminarily explain to us why a blind study is a useful tool in scientific research.

A. Well, a blind study -- there are two kinds of blind studies. In this case it's the patient that is blinded.

In other words, the patient is reporting symptoms, but the patient doesn't know whether there's an electromagnetic field or not.

Other blind studies would be somewhat different, whereas the investigator doesn't know if the subject is in the control group or the exposed group, but that it's extraordinarily important to have a blinded study because otherwise there's every possibility for bias.

So, this is a study in which the subject was documented of expose -- of experiencing temporal pain, headache, muscle twitching, and skipped heartbeats when the fields were on.

Now, what they did was they -- first of all, this was a female physician, and she had brain scans for all kinds of things, so her health was well documented. She was, I believe, 40 years old, so she was not old.

And she was put in a place where she had two ELF -- EMF projectors on either side and they altered between applying a pulsed electromagnetic field or just not having the thing on at all.

And she was in this place where she had a button to push saying yes or no. Yes, it hurts; no, I don't feel anything.

And the critical evidence is shown I guess in table five, where you can see that -- no, that's not the one I mean. She -- that's whether or not she could determine whether the field was on or off.

Look at the bottom of table three and the bottom of table four. So, in the sham conditions or when the exposure was mild she felt nothing. She had no symptoms. When the pulsed field was on and was strong, 10 out of 10 times.

Just a minute. Am I reading this right? I believe that's correct.

And then in table four they were looking at continuous versus pulsed fields. The continuous field she was less able to distinguish than the pulsed fields.

And one of the conclusions of the study is that it's the on and off that is particularly important in triggering the symptoms.

Q. And the symptoms are listed in table four? Are some of the --

A. Yes. Headaches are the major ones, temporal pain, muscle twitches, mild headaches, some combination of those three things.

Q. I need a minute to consult with my colleague here. I'm sorry, one other question.

The continuing field was the other table?

A. Continuous field is table four, and in part B of table four you can see that the continuous field she got three out of five right.

Q. Okay. But there --

A. Whereas with the pulsed fields she got five out of five right, right being the sense that she had symptoms when it was on.

Q. Okay. But to some extent the symptoms did continue in the continuous field?

A. Yes.

MR. SEYMOUR: All right. Let me consult with my colleague and I may turn it back to you.

Q. There's one other topic that we came close to. It may have been involved in the mammogram, abnormal mammogram.

Can you tell us what the role of melatonin is, A, in normal operation and, B, as shown in the setting of EMFs and some of the research studies that have been made of it?

A. Melatonin is a hormone that is released by the pineal gland and is very much related to normal circadian rhythms, the sleep-wake cycles, that almost all mammals have. And it is -- there's a large body of evidence that exposure to electromagnetic fields disrupt the normal cycling of melatonin.

Now, if the normal cycling of melatonin is disrupted, it follows that the sleep-wake cycles are disrupted. And there is a body of evidence that suggests this may be one of the mechanisms underlying both the electrical hypersensitivity syndrome and possibly even having a correlation with breast cancer.

It -- I think the evidence even in animal systems that EMFs disrupt melatonin is very strong. It's less strong in people, but the multiple reports of sleep disturbances are certainly consistent with disruption of melatonin.

Q. And does melatonin have some beneficial effect on the human body?

A. Well, it's certainly important that we get a good sleep every night. Melatonin is a hormone. It almost certainly does many other things as well, but regulation of sleep is the most important. And a lot of the other things associated with abnormal melatonin probably follow from the disruption of sleep-waking cycles.

Q. One obvious question: Do you know if melatonin plays any role in protecting against the development of breast cancer? Are there studies that seem to indicate that?

A. Yes. There are studies that suggest it's well known that women that work on shifts are elevated risk for breast cancer. And shift work disrupts the normal cycling of melatonin.

I go to Korea on Sunday, and I know that my sleep-wake cycle will be totally screwed up for a couple of weeks. And that's because of melatonin.

Q. Yes. I meant to ask you. You were asked during your direct about your job and what your function is.

Can you just give us a little idea of what your responsibility and duties are in connection with keeping up with the science and this and other areas that affect the general public widely?

A. Well, you know, I'm a professor at a university, which means that I have teaching responsibilities. And for years I've taught the graduate introduction to environmental health class.

I do a lot of teaching in other classes in the neurosciences. I teach lectures on Alzheimer's disease, on neuronal mechanisms of learning and memory.

But my research time is pretty much my own direction. I should emphasize I've never done EMF research. My EMF involvement has always been administrative or reviewing.

I search for my own funding for research. It's been primarily focused around health effects of exposure to persistent organic compounds like dioxins and PCBs, air pollution, the effects of air pollution.

I have current grants on effects of contaminants on menstrual hormones in young women, on exposure to contaminants with Alaska native population, of issues around health hazards of drinking water problems in Uganda. We have just finished a project on air pollution in Pakistan.

So, it isn't that those are assignments, but those are important and interesting scientific questions that I choose to pursue.

Q. And if I recall correctly, we had to terminate our discussion yesterday afternoon so you could go over to Lennox, Massachusetts to participate in a panel on yet another area of public health.

A. Yes. That was an interesting panel. The question was -- I usually am invited to talk about human health effects of environmental contaminants. This time it was what are the effects of environmental contaminants on wildlife. And animals are -- have most of the same genes that we have.

Q. And some of them are nicer.

A. Some of them are nicer.

MR. SEYMOUR: Mr. Fitzgerald, have you got any redirect?

MR. FITZGERALD: Yes. I have redirect.

MR. SEYMOUR: If it's five minutes why don't we take a quick stretch and walk down the hall.

MR. FITZGERALD: Sure.

VIDEOGRAPHER: The time now is approximately 2:31 and we are now going off the record. And this represents the end of tape three of today's deposition.

We are now off the record.

(Recess taken.)

VIDEOGRAPHER: The time now is approximately 2:43. We are back on the record. This is the beginning of tape four of the deposition of David O. Carpenter, M.D.

We are now on the record.

BY MR. SEYMOUR:

Q. Dr. Carpenter, do you have an opinion, with a reasonable degree of certainty, that the various conditions that we identified during our discussion of Defendants' Exhibit E, including such things as headaches, sleep disruption, pain, uncontrolled vomiting, nervous system disruption, balance problems, and the others, that those were all caused by -- more likely than not caused by the exposure over 20 years to high levels of EMF in Mrs. Barnett's home?

MR. FITZGERALD: Objection to form.

THE WITNESS: It is my opinion that it is more likely than not that those symptoms that I identified were caused by Mrs. Barnett's exposure to elevated magnetic fields over those periods.

BY MR. SEYMOUR:

Q. Then the related question. After seeing the findings from the Arizona University neurological institute, see if I got the name right, Arizona Health Sciences Center Department of Neurology, that you have an opinion, with a reasonable degree of certainty, that the overall condition that Mrs. Barnett has been suffering from is, in fact, electro hypersensitivity, known as EHS, as a result of her exposure to the EMFs?

A. That is correct. It is my opinion that she suffers from most of the symptoms that have been described as electro hypersensitivity.

Q. And is it more likely than not that the EHS was caused by 20 years of exposure to EMFs in the range of 20 to 30 milliGauss?

A. Yes.

MR. FITZGERALD: Objection to form.

THE WITNESS: It is.

MR. SEYMOUR: Mr. Fitzgerald?

FURTHER EXAMINATION

BY MR. FITZGERALD:

Q. Dr. Carpenter, you recently received this report from Dr. Hishaw which has been marked as Defendants' --

MR. SEYMOUR: Exhibit G.

BY MR. FITZGERALD:

Q. G, correct?

A. Yes.

Q. When did you receive it?

A. I don't recall precisely. Perhaps a month ago.

MR. SEYMOUR: Isn't there an e-mail?

BY MR. FITZGERALD:

Q. We might have something here that will refresh your recollection.

A. March 27th, not very long ago.

MR. SEYMOUR: Same day you received it.

BY MR. FITZGERALD:

Q. Is it the case, Dr. Carpenter, that until you received that report you were prepared to testify that Mrs. Barnett suffered from Alzheimer's disease and that you knew the cause. It was EMF exposure. Right?

A. Well, I'm not sure I would have testified to that because, you know, she did not come with a physician's diagnosis of Alzheimer's. She came with her self-report of Alzheimer's.

So, I think I had the same concerns that Dr. Sobel had when he requested that she be seen by a neurologist. Now, at the time I wrote the report in, what, last August or September, something like that, I had very little information of...

Q. Go ahead.

A. Well, I'm just not sure how strongly I would have come down on the Alzheimer's disease. I think I probably would have said that these rather non-specific symptoms are frequently characteristic of Alzheimer's. Lack of sleep, alteration of circadian rhythms, some memory loss, these are classical symptoms of early Alzheimer's, but only of early Alzheimer's.

Q. Okay. In your declaration -- you understand that the declaration that is filed in the case is supposed to be a disclosure of what your opinion is that you're going to testify to.

A. Yes.

MR. SEYMOUR: I object to the form of the question unless you put in as of the date the declaration is signed.

BY MR. FITZGERALD:

Q. When you signed this declaration you said -- I just lost this. "I have reviewed the amended complaint and its exhibits and also Mrs. Barnett's deposition and her medical records in order to render this opinion."

And then the opinion you rendered was, "Mrs. Barnett suffers from probable Alzheimer's disease with significant memory loss and disruption of nervous system function which are either caused by or made worse as a consequence of her chronic exposure to magnetic fields."

That was your opinion, correct?

A. That was my opinion.

Q. Now, you've told us -- and I go back to my previous question -- if you were not given a copy of Dr. Hishaw's report that would have continued to be your opinion.

A. Correct.

Q. Now, since you saw Dr. Hishaw's report, you decided that these symptoms must be due to her magnetic field exposure in some other respect, right?

A. Well, we went through that other paragraph. Actually, I had forgotten that that other paragraph about memory loss was in my report. Those were the specific complaints she had, and I was considering those.

Now, those are features of Alzheimer's disease, of early Alzheimer's. I don't apologize for that report in any regard. The report was based on the symptoms that she reported.

The -- now, the diagnosis was self-reported, but the symptoms are consistent with Alzheimer's, except that on careful neurologic exam she does not have Alzheimer's.

Q. Was she examined by neurologists and neuropsychologists before Dr. Hishaw examined her?

A. Yes, she was.

Q. And were the results of those examinations made available to you?

A. Well, yes. I have them.

Q. And did any of those physicians diagnose Alzheimer's?

A. No, they didn't diagnose Alzheimer's. They all commented on her memory loss, her headaches, her pain.

Q. Nevertheless, you were prepared, based on her self-report, to testify that she had Alzheimer's.

MR. SEYMOUR: Probable Alzheimer's.

BY MR. FITZGERALD:

Q. Probable Alzheimer's.

A. Yes, the emphasis on probable.

Q. And you were prepared to testify that that condition of probable Alzheimer's was probably caused by her magnetic field exposure.

MR. SEYMOUR: No. Object to the form. That --

MR. FITZGERALD: Go ahead.

Your objection is noted.

BY MR. FITZGERALD:

Q. Go ahead, answer the question, please.

A. Can you repeat the question?

MR. FITZGERALD: Can you read the question back.

You don't need to object again.

(Whereupon the record was read.)

THE WITNESS: Correct.

BY MR. FITZGERALD:

Q. And once you received Dr. Hishaw's report you decided that her condition must be due to EMF exposure through another pathway, with this hypersensitivity that you're talking about. I mean that's just a fact, right?

A. Again, go back to the paragraph in my report about memory loss and forgetfulness or whatever it was. Those are her symptoms, and I acknowledged those symptoms.

I said probable Alzheimer's. At the time I prepared that report I actually did not use the word "electro hypersensitivity" because I wasn't convinced that it had been -- that the weight of evidence had convinced me it was a real syndrome.

Q. And then after you got Dr. Hishaw's report you decided that that cluster of symptoms was due to hypersensitivity.

A. No. That's not quite accurate. It was a combination of Dr. Hishaw's report, and the major factor was the appearance of this publication which I received only a few weeks ago from a reputable lab, in a very good controlled condition, which gives me confidence that I can speak in an era like this about more likely than not that this is electro hypersensitivity.

Without that paper I would not have made those allegations.

Q. Bust just as a --

A. That is more important than the --

Q. I'll talk to you about that in a moment, but just as a matter of chronology, it was after Dr. Hishaw's report came into your hands, and you found that she did not have probable Alzheimer's, that you then concluded that her symptoms were probably due to another syndrome associated, you believe, with magnetic field exposure?

MR. SEYMOUR: Asked and answered.

MR. FITZGERALD: No. He hasn't. That's all I'm trying to do is to get that. It's just a temporal question.

BY MR. FITZGERALD:

Q. That's correct.

A. Yes.

Q. Now, this article, which you say just came into your possession a few weeks ago, has a publication -- no. That's the received date. The publication date is -- copyright 2/11.

Do we know when it was published? It's got 2/11 copyright, but International Journal of Neuroscience 121 pages 670 to 676.

Someone could --

A. Isn't that a 2012 publication date.

Q. I don't know. That's what I'm asking you. I can't find a publication date on the front page, anyway.

A. No. It's 2011. You had it right. It's in the upper right-hand corner.

Q. That's a copyright date. Is that the same --

A. No, but below -- the last line is the journal, the pages, the volume. It's 2011.

Q. Right, doesn't tell us when in 2011.

A. No.

Q. Sometime in 2011.

A. But in any case, I didn't -- I was unaware of that paper until it was sent to me by a colleague from Montreal a couple of weeks ago.

Q. Who was that?

A. Andre Fosteau.

Q. This -- I haven't had time to read this paper, but as you described it it sounds like it was an experiment on a single individual.

A. That's correct.

Q. And has the experiment been replicated?

A. No.

Q. Is there any significance in whether or not experiments like this can be replicated or not?

A. Well, it's certainly important in all science to have replication. It would be very difficult to replicate this exactly because the EHS syndrome does not show exactly the same expression in all individuals.

Q. And this is just a question of words. When I think of hypersensitivity I think it's something that you have. It's a condition that you have that makes you particularly susceptible to a condition rather than something that is caused by that condition.

Do you see what I'm saying?

A. Yes. I might not disagree with you on that.

Q. So that --

A. This World Health Organization document has a nice description. I believe they say this -- there are -- a more general term for sensitivity to environmental factors is idiopathic environmental intolerance.

Q. Okay.

A. And I think what you're getting at, which I do agree with you, is that EHS is not something that everybody is vulnerable to. Some people are more vulnerable than other people. But that doesn't make the syndrome any less real.

The implication here is that somebody -- some people develop allergies to poison ivy. Other people do not. This particular

person, Mrs. Barnett, has all of the classic symptoms, or almost all of them, of electro hypersensitivity, and it has disrupted her life.

Q. Just a second. There aren't any classic symptoms of electro hypersensitivity, are there? I mean --

A. Read what WHO says, what is EHS. It's non-specific symptoms. They include dermatologic symptoms like redness, tingling, and burning sensations, as well as neurasthenic and vegetative symptoms, fatigue, tiredness, concentration difficulties, dizziness, nausea, heart palpitations, and digestive disturbances.

And this is a summary document of -- at this point the World Health Organization is somewhat skeptical that it's a real disease, but that I would take to be the classic symptoms of electro hypersensitivity.

Q. The classic symptoms of a non-disease.

MR. SEYMOUR: Object to the form.

THE WITNESS: The disease that at this point was not well documented but now is.

BY MR. FITZGERALD:

Q. The RAPID series of studies that you were asked about, that took place over a period of years, right?

A. Correct.

Q. There was something like $65 million in funding spent on them.

A. And much less impact than the five million that we had in the New York Powerlines Project.

Q. And what was the end point of that effort?

A. Well, the end point was a document that was published by NIHS that basically acknowledged that there were significant -- statistically significant relations in human studies which they had not supported, that basically concluded we don't know enough to determine whether or not there is a hazard based on two major factors.

We don't know, A, mechanism, which we have talked about extensively today, which I think is no reason for anything. And secondly, that there's no animal model, in other words, that you don't get leukemia in mice.

And I also don't agree with that conclusion because the -- what we know is mostly about induced currents. And induced currents in a four-legged animal that's small are very different than the larger two-legged animal like humans.

Q. Just one question about what you meant in your answer. You said that they acknowledged results from human studies that they had not supported. By --

A. They did not provide the money for that is what I meant.

Q. Okay. When you reviewed the medical records provided to you and saw that there were no diagnoses of Alzheimer's disease or probable Alzheimer's disease from any of the treating physicians, why did you decide to accept Mrs. Prescott's self-report of Alzheimer's for the purpose of forming your testimonial opinion?

A. Well, I think that's a good question, but the answer is that the symptoms that she consistently reported are totally consistent with early Alzheimer's. And, you know, maybe it was just responding to her suggestion, but those symptoms are characteristic of early Alzheimer's.

Q. Is it characteristic for an Alzheimer's sufferer to have those symptoms continuously over a period of 20 years?

A. Well, Alzheimer's patient will have those symptoms for a period of maybe five years, especially if they're relatively young with early onset. An Alzheimer's patient will get worse. That it's never reversible.

Q. Typically, the typical course of Alzheimer's from the first manifestation of the mild cognitive impairment to death is ten years, isn't it?

A. I think it's actually sometimes even shorter than that. But, you know, again, it depends on the age of onset. My partner's wife died of Alzheimer's last fall. She had Alzheimer's for 15 years and she had very much these symptoms at the early onset.

And then the last eight years of her life she was in a nursing home and knew nobody.

Q. But --

A. But it was a constant downhill progression.

Q. Well, Mrs. Barnett attained a disability determination in 1992 based on these symptoms.

Wouldn't it be an extraordinary outlier for her to be in the condition that was described at the time of her deposition, which was more than -- well, it was approximately 20 years later than that?

A. No. I agree with that. That would be extraordinary. But also the fact that she was given that disability -- that was allowed as a disability gave me some confidence in that these were real findings.

They weren't just her imagination. That you don't get a disability allowance if you're just reporting that your memory function isn't that good.

Q. Now, did you review the reports of the two neuropsychologists who had examined her over the years, Dr. Brooks and Dr. Delaney?

A. I skimmed them. I didn't review them in great detail.

Q. Well, you recently, today, gave an opinion that had to do with her improving, her condition improving, since she was out of high magnetic field environment.

Did you make any effort to compare the description of her condition by Dr. Hishaw with the descriptions in those earlier neuropsych reports?

A. No. I did not go back to review those earlier ones again, but I was certainly impressed -- I should have done that, but I was certainly impressed that Dr. Hishaw's description did not sound like this was a disabled woman at all.

Q. When you learned or when you received Dr. Hishaw's opinion, did you consider whether the plaintiff's complaints might be due to something other than EMF exposure?

A. Yes. I think that's been part of my consideration all along, is this just a psychotic woman.

Q. Well, that's one possibility, but aren't there others?

A. Well, the real issue here is are all of these symptoms psychological or do they have some environmental basis.

And I think that the weight of the evidence suggests that it has an environmental basis, primarily on the matching of her symptoms. You don't like my use of the word "classical," but whatever the World Health Organization described as being EHS, that's what she fits.

Q. But isn't the question whether her symptoms are due to something in the environment, or psychological, or caused by some other medical condition?

A. Yes. That's an appropriate concern.

Q. You have no qualifications, professional qualifications, in psychiatry, do you?

A. No.

Q. Or psychology?

A. No.

Q. Or in veterinary medicine?

A. Well, I'm a farmer. I have a little experience in veterinary medicine. And I just returned last night from -- yesterday from my daughter, who is a practicing veterinarian. So, I have veterinary consult.

Q. So that's as close as you get.

A. My son-in-law is also a veterinarian.

Q. As long as we're on that subject, you don't know, I gather, what the cause of death of these various pets -- strike that.

You don't know what the causes of the deaths of the various pets that Mrs. Barnett had were.

A. All I know is the report -- I think there were the three dogs. One was reported to have died of cancer. One was reported to have died of unknown causes. I know nothing beyond that.

Q. Do you know the ages at which the dogs died?

A. No, I don't. And I also don't know how many -- that's an awful lot of dogs for a relatively brief period of time. I don't know whether she had more than one dog at a time or whether it was that the dogs didn't live long when they lived with her.

Q. What period of time do you think we're dealing with here?

A. I actually don't recall from her deposition.

Q. Well, one of those dogs actually lived most of its life in another address. Does that have any significance to you?

A. Well, depends on how much of its life he lived in the Connecticut address because, again, as we talked about with human cancer, there's a latency between exposures and develop an expression of almost any kind of cancer.

Q. There was a set of measurements or a measurement report, Defendants' Exhibit F. Speaking of latency periods, you gave some testimony about a five-year latency period.

Are you assuming that the magnetic field environment at Mrs. Barnett's home was as indicated by that exhibit, by those measurements throughout the time of her residence there until she moved in 2009?

A. Am I assuming that those were typical?

Q. Yes.

A. I think the answer to that is yes.

Q. For that entire time.

A. I have no other explanation. I have no other evidence, but I'm assuming that these were typical from the time that the line was upgraded.

Q. Until she moved?

A. Until she moved.

Q. There's a reference to an abnormal mammogram. Can an abnormal -- the report of an abnormal mammogram be caused by something other than a tumor?

A. Other than?

Q. A tumor.

A. Oh, absolutely, yes.

Q. There are many things that can show up that will cause the test to be labeled abnormal and you don't really know --

A. That's correct.

Q. Knowing only that, you don't know what the cause of the abnormality was or even if it was an artifact, right?

A. That is correct.

Q. Suppose that Mrs. Barnett had severe and chronic headaches for years before she moved into her Trumbull house. Would those have been due to magnetic fields exposure in the Trumbull house?

A. Headaches that she had before she moved in, no.

Q. Right.

A. Depends, of course, on where she was. But, again, we have no information on her frequency of headaches before she moved in.

Q. But if she had headaches after she moved in you would say they were due to her EMF exposure.

A. Well, in conjunction with the other symptoms, yes, I would say that they are due to the MF exposure.

Q. What significance, if any, is the fact that she had severe chronic headaches, assuming this is the case, before she moved in? Is it just irrelevant?

A. I know of no evidence that she did have severe chronic headaches before she moved in.

Q. Okay. If she did have -- if her medical records reported severe chronic headaches for years before she moved in, would that have any significance to your opinion?

A. Yes, it certainly would. It would reduce dramatically my belief they were secondary to the EMF exposure.

Q. I can't remember what you said about loss of balance, or balance problems is how it's described here.

A. That is consistent with the EHS syndrome, which is associated with some motor dysfunction of -- that's not stated there. But balance would not be what I would characterize as being the most typical, but it's a reflection of nervous system dysfunction.

Q. You know that Mrs. Barnett had one or more strokes as a young woman?

A. No, I did not know that, no.

Q. And do you know that she had some balance problems when she had stroke -- when she had the stroke?

A. If she had a stroke I would not be surprised she had balance problems.

Q. And if that were the case would you hesitate to ascribe her balance problems, to the extent they exist, to EMF exposure?

A. Well, yes, I would, but I don't recall any evidence she had strokes.

Q. Well, if you read those -- unless you got a different set of medical reports than I did, you can find it there.

A. It's been a while since I reviewed those, but...

Q. Now, do you know which of these quality-of-life issues -- and I'm referring to Exhibit E in the list of complaints under quality of life.

Do you know whether any of them have been identified as classic symptoms or side effects of lupus?

A. I don't think any of them have been identified as classic symptoms of lupus.

Q. Including --

A. Again, I have a sister-in-law with lupus. I know a fair bit about the disease. Perhaps fatigue is common in lupus.

Q. Here we -- going back to Dr. Hishaw's report -- we find him saying on the last page, "Certainly, Mrs. Barnett has several other reasons to experience cognitive difficulty. She has chronic pain issues and this can often lead to complications in cognition. Additionally, her pain symptoms lead to sleep disruption. Cognitive difficulties are commonly associated with sleep disturbance. She has been treated for hyperthyroidism with no recent thyroid evaluations. Hyperthyroidism has been associated with cognitive difficulties.

"Lastly, the patient has a possible history of central nervous lupus. Cognitive and behavioral changes have been described with central nervous lupus.

"Given her history of repeated aseptic meningitis and possible stroke, further evaluation in this area may better describe some of the cognitive difficulties that Mrs. Barnett has noticed over the years."

Now, does that information cause you to reconsider whether the explanation of these symptoms, if it's not Alzheimer's, must be -- nevertheless be magnetic field exposure?

A. It's very important to say possible stroke, because I saw nothing in the medical records that indicated it was a stroke. There were -- I guess you can talk more about that because I don't recall specifically. But the reports of ischemic episodes or something like that, very common, it almost never is a stroke.

You know, it's certainly true if there is well documented stroke that that can lead to a variety of cognitive functions. It can lead to, depending on what part of the brain it is, balance problems.

But her symptoms, to the best of my knowledge, did not occur until after she moved into this house, after the line was

upgraded so that the magnetic fields were really extraordinarily high. I mean 20 to 30 milliGauss is enormous.

And the symptoms that she has are consistent with electro hypersensitivity. So, I have no difficulty in finding that that meets the more likely than not criteria.

Q. Unless -- so the only -- so you are prepared to find that anything she complains about is -- that falls within symptoms that have been associated with this syndrome must be caused by her magnetic field exposure unless it can be proven to you that they preexisted her moving into the house, or that they are associated with some other condition, such as her lupus, which is not associated with magnetic field exposure.

A. I think that's an accurate statement. Unless there is some other explanation that makes medical sense, given that we have strong evidence that exposure to magnetic fields causes, in vulnerable people, not in everybody but in vulnerable people, those symptoms, then I'm prepared to say that it's more likely than not that they are due to her long-term exposure to magnetic fields.

Q. Would you accept the plaintiff's self-report of stroke?

A. No.

Q. Why would you not accept her self-report of stroke when you accepted her self-report of Alzheimer's?

A. Well, I didn't really accept her self-report of Alzheimer's.

Q. You --

A. I said probable Alzheimer's. And I emphasized the symptoms that she reported, which were poor memory and poor attention.

Q. You said -- you did that on the basis of her self-report.

A. The probable Alzheimer's was on the basis of her self-report. I did not say Alzheimer's. I said probable Alzheimer's. That's a major difference.

Q. On what do you base your conclusion that the -- well, being unfair.

Have you concluded or do you assume that the plaintiff's condition has improved since she moved to Arizona?

A. I'm really assuming on the basis of incomplete evidence. The evidence is definitely incomplete.

Q. And what evidence is that?

A. Well, the -- Dr. Hishaw's report, if that's his name. What one would like to have had was the same analysis before she moved to Arizona. The -- I'm reading between the lines.

Q. What are you comparing? You've got a condition described in Dr. Hishaw's report. What are you comparing that to?

A. To the report of the neurologist -- I've forgotten which one was the neurologist -- and the psychiatrist that she had seen before that are in all of these records which I skimmed through. And every one of them, whether it was the neurologist or psychiatrist, they all referenced her mental state, her fatigue, all of these symptoms.

Now, I understand that those are her report to them, and they're basically regurgitating it, but they are stating things that seem much worse that's in the Hishaw report.

Q. That's your impression, but you haven't made a close comparison.

A. That's absolutely correct.

Q. When did you advise Mr. Seymour that your opinion concerning Mrs. Barnett was changing?

A. I've had no personal contact with Mr. Seymour until yesterday for many months. I think actually we never met until yesterday.

Q. Once you got the report of Dr. Hishaw --

A. It was March 27th.

Q. March 27th. And you read it. You had no communication with Mr. Seymour or Ms. Seymour about your reaction to it?

A. No.

Q. They did not inquire about your reaction to it?

A. No.

MR. FITZGERALD: No further questions.

MR. SEYMOUR: Okay. Let me consult with my colleague. With any luck we'll let you go, but don't hold your breath.

Off the record.

VIDEOGRAPHER: The time now is approximately 3:29 p.m. We are off the record.

(Off the record.)

VIDEOGRAPHER: The time now is approximately 3:33 and we are back on the record.

FURTHER EXAMINATION

BY MR. SEYMOUR:

Q. Dr. Carpenter, I may have misheard Mr. Fitzgerald, but I thought I heard him ask you whether Mrs. Barnett had these symptoms that are described in that excerpt from the complaint for all 20 years she was there. It sounded to me as if he asked that and you answered it on that assumption.

Am I wrong?

MR. FITZGERALD: I asked him if he assumed that her exposure, the EMF exposure when she was there the entire time she lived in the house was as shown on the exhibit.

MR. SEYMOUR: Okay. Fair enough.

BY MR. SEYMOUR:

Q. On the subject of lupus, do you have enough familiarity with lupus to be able to answer these questions?

Do you know if lupus causes sleep disruption?

A. I have no information that it does.

Q. Do you know if lupus causes a pain syndrome?

A. No, it does not.

Q. Do you have any knowledge that -- whether lupus causes endochondroma tumors?

A. Does not.

Q. Do you know if lupus causes bone hotspots?

A. Does not.

Q. Do you know if lupus causes uncontrolled vomiting?

A. Does not.

Q. Do you know if lupus causes gastrointestinal disturbance?

A. No.

Q. Do you know if lupus causes anxiety for the health of one's children?

A. No. Lupus is not contagious.

Q. Do you know if --

A. Although I should say that lupus can be a very serious disease and a mother with lupus might worry about her children because of her being disabled and not be able to care for them.

Q. But that's a secondary effect.

A. Secondary.

Q. It's not a medical effect.

Do you know if lupus causes a fear of cancer?

A. No. It does not.

Q. Do you know if lupus causes fear of cancer in children?

A. No. It does not.

Q. Do you know if lupus causes death of pets?

A. It does not.

Q. Do you know if lupus causes loss of professional skills?

A. Lupus can be sufficiently disabling that it interferes with one's work schedule, but it doesn't cause loss of professional skills.

Q. All right. Do you know if lupus causes abnormal mammograms?

A. No. It does not.

MR. SEYMOUR: All right. I think that does it. And I thank you very much.

VIDEOGRAPHER: The time now is approximately 3:36. And this concludes tape four of the deposition and closes out our deposition of Dr. Carpenter.

We are now off the record.

(Deposition concluded at 3:36 p.m.)

CAPTION

The Deposition of Arthur O. Carpenter, M.D., taken in the matter, on the date, and at the time and place set out on the title page hereof.

It was requested that the deposition be taken by the reporter and that same be reduced to typewritten form.

The Deponent will read and sign the transcript of said deposition.

CERTIFICATION

STATE OF___________________________________

COUNTY/CITY OF______________________________

Before me, this day, personally appeared David O. Carpenter, M.D., who, being duly sworn, states that the foregoing transcript of his/her Deposition, taken in the matter, on the date, and at the time and place set out on the title page hereof, constitutes a true and accurate transcript of said deposition.

____

SUBSCRIBED AND SWORN to before me this__________ day of ________, 2012, in the jurisdiction aforesaid

____

My commission Expires

DEPOSITION ERRATA SHEET

RE:

FILE NO.

CASE CAPTION:

DEPONENT:

DEPOSITION DATE:

To the Reporter:

I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me. I request for the following changes be entered upon the record for the reasons indicated. I have signed my name to the Errata Sheet and the appropriate certificate and authorize you to attach both to the original transcript.

....

....

SIGNATURE: ________________________

DATE: ________

INDEX

WITNESS: DAVID O. CARPENTER, M.D.

EXHIBITS

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CARPENTER DEPO EXHIBIT 19

2016 WL 5395125 (D.Mass.) (Partial Expert Testimony)
United States District Court, D. Massachusetts,
Worcester Division.

G, a 12-year-old minor suing by a fictitious name for privacy reasons,: Mother and Father, suing under fictitious names to protect the identity and privacy of G, their minor child, Plaintiffs, v. THE FAY SCHOOL (by and through its Board of Trustees) and Robert Gustavson, Defendants.

No. 15-cv-40116-TSH.
May 23, 2016.

Deposition of David O. Carpenter, M.D.

Name of Expert: David O. Carpenter, M.D.
Area of Expertise: Medical & Surgical >> Hospital
Area of Expertise: Medical & Surgical >> Public Health
Area of Expertise: Medical & Surgical >> Toxicology
Representing: Plaintiff
Jurisdiction: D.Mass.

10:00 A.M.

SCHWARTZ HANNUM PC

11 Chestnut Street

Andover, Massachusetts 01810

Linda S. Pezza, CSR

WARROOM, DSI

103 Dyer Street

Providence, Rhode Island 02903

401.621.7300

[Note: Pages 2-11 missing in original document]

Q Okay. And then did you come back to Harvard Medical School?

A That's correct.

Q Did you graduate from Harvard Medical School?

A Yes, I did.

Q And what year did you graduate?

A 1964. (MR. MARKHAM LEFT ROOM)

Q And did you receive an M.D. from Harvard?

A That's correct.

Q Were you ever licensed to practice medicine?

A No, I chose not to intern and went back into the laboratory continuing my research. My thought at the time was I would do research until my brain got sort of dead, and then I would go back and practice medicine. I never have gone back.

Q So it's fair to say that you're not licensed to practice medicine in any jurisdiction?

A That's correct.

Q Did you ever complete a Medical Residency Program?

A No, I did not.

Q Did you ever complete a Medical Intern Program?

A No, I did not.

Q Are you licensed to diagnose patients?

A No, I am not.

Q Are you licensed to treat patients?

A No.

Q I'm sorry?

A No.

Q Can you prescribe medications?

A No.

Q Can you prescribe specific treatment to patients?

A No.

Q Can you prescribe any diagnostic tests to patients?

A No.

Q Is it fair to say that your clinical medical experience is limited to what you received as a medical student?

A Well, yes and no. In my hands-on experience examining patients and treating patients, that is correct, but my research has increasingly focused on studies of causes of human disease, which is very much built on my medical training. So, it's not the clinical practice, but it's studying origin and causes of human disease.

Q Okay. So when it comes to patients, you don't have any clinical medical experience?

A That's correct.

Q Are you Board Certified in any medical field?

A No.

Q In your professional career, have you primarily held administrative and laboratory positions?

A Yes, that would be correct, combination of administrative and laboratory at the same time.

Q Are you an engineer?

A No.

Q Do you have any engineering background?

A None whatsoever.

Q Are you a professional engineer?

A No.

Q Is it fair to say that you don't have any experience in engineering?

A Yes.

Q Now, the incident matter that you're here to testify about, I believe involves electromagnetic fields at the Fay School, would you agree with me there?

A Yes.

Q So today, I expect that we're going to be talking a lot about electromagnetic fields, and when doing so, I'd like to refer to that term as "EMF," will you understand what I mean when I use that term?

A I certainly will, yes.

Q Okay. And we're going to be talking about the Fay School a lot today, and what I'd like to do is just use the term either "Fay" or "the School," is that fair enough?

A That's fine.

Q Okay. Have you conducted any studies of your own on EMF's?

A Well, yes, I have in the sense that I supervised and administered studies for the New York State Power Lines Project, which was a major project funded by New York State Utilities beginning in 1982 and ending in 1987. So, I was the overall Executive Secretary of that project, which meant that I supervised research, helped to identify research questions that needed to be explored. The research projects included human health studies, animal toxicology and major engineering analysis of exposures -- measurements of EMF's. These were power line fields, primarily, not radio frequency fields. Again, I was not

the lead researcher in those projects, but I certainly had a major role in the performance of those studies.

Q Did you conduct any of the actual research?

A No.

Q And you said there was a major engineering analysis; is that correct?

A That's correct.

Q Did you conduct any of the major engineering analysis?

A No, I did not, I supervised it. As I said, my expertise is not the engineering components, and we had three members of our Board that were primarily engineers that helped to design the exposure systems, measure the fields in the studies, and basically, be responsible for the engineering aspects of our program.

Q Okay. Now, you prepared a report in connection with this litigation; is that correct?

A That is correct.

Q Do you recall stating in that report that your personal research has not been directed at electromagnetic fields?

A That's correct, yes.

Q Okay. Is that a fair statement, that your personal research has not been directed at the study of electromagnetic fields?

A That is correct. I mean, as I said, I've had senior administrative responsibility, which got me very intimately involved in those studies, but I wasn't the one that actually did the studies.

Q Okay. And that would be true for the work that you've done throughout your career, that you've never actually conducted the research --

A That's correct.

Q -- for those studies?

A That's correct.

Q Have you ever taken EMF measurements?

A Yes, I have.

Q Okay. And do you have any -- strike that. When have you taken EMF measurements?

A Well, I have both a 60 hertz monitoring device and a radio frequency monitoring device. I've been filmed taking such measurements around my office and in my home. This was to report the intensity of the magnetic fields or the radio frequency fields in relation to the distance from devices that would generate such fields. It was not for research purposes. Some of these were measurements I conducted within my own home, especially in relation to my child's bedroom, where I took my meter and found that the side of the room where the bed was on had much higher magnetic fields than the other side of the room, and we simply moved the bed to the other side of the room.

Q Have you ever conducted EMF measurements for the purpose of any research project?

A Not really directly. I have published a major paper on EMF measurements with one of the colleagues that is

[Note: Pages 18-48 missing in original document]

Q Can you turn to the second page of the report? Are you there?

A Yes.

Q Do you see on the second page, you mention the precautionary level proposed by the BioInitiative Report?

A Yes.

Q And it looks like you're referencing the 2007 level; is that correct?

A That is correct.

Q And that would be 0.1 microwatts per centimeter squared?

A That's correct.

Q And we established a few moments ago that that's 10 times lower than the FCC guidelines?

A That's much more than 10 times lower.

Q I'm sorry, 10,000 times lower?

A Yes.

Q Why do you mention that level in this report?

A Because that's what I published as a precautionary level, and notice I do not use the word "standard," I never proposed that as a standard, but a precautionary level below which there should be no measurable adverse health effects.

Q As part of your expert opinion, have you been retained to opine on the level that Fay School must achieve

[Note: Pages 50-67 missing in original document]

G[Text redacted in copy.] does have EHS.

Q And what do you base that on?

MR. MARKHAM: Objection, that's not -- he didn't answer your question. I'll stipulate, we're not going to have him give an opinion on whether G[Text redacted in copy.] has EHS. He's never examined G[Text redacted in copy.], we've made that clear. His testimony, as is in the report and as I designated, if this will help you with focusing your examination, not that it was unfocused, I'm just saying this will just narrow it, he's going to testify that EHS is a recognized syndrome in certain individuals when they are exposed to WiFi radiation and other types of radiation, that there is -- that there's credible scientific data upon which his opinion to that effect is based. He's also testifying, based upon his knowledge and readings, it is medically plausible that, as a general proposition, EHS in some people can be caused by exposure to EMF. Those are the only two things he's testifying about, not about the actual levels in the school, whether Dr. Maret's peaks are valid or not. We're not getting into that with him. We won't be asking those questions.

MS. McKEAN: Just so I'm clear --

MR. MARKHAM: Let me just finish.

[Note: Pages 69-74 missing in original document]

Q Now, this case doesn't involve cell phone use, correct?

A Correct.

Q This case involves the wireless system at Fay School, correct?

A Correct.

Q In your opinion, is there any increase risk of cancer with respect to wireless networks at schools?

A Yes.

Q And is your belief consistent with the mainstream scientific community's belief?

A I don't think that the mainstream scientific community goes so far as to be excessively concerned about WiFi, but the WiFi radiation is very, very similar, differs somewhat in frequency, to that from cell phones, and it is very clear to people that understand the differences that, yes, there's going to be an increased risk of cancer from WiFi, depending on the intensity of the radio frequency radiation, and the duration of time that individuals are exposed to it. The brain cancer studies really only show elevations in brain cancer in adults if they've been using cell phones intensively for 10 years or more. So, the studies have not been done with WiFi, nor would it be very easy to document individual's 10 year exposure to elevated WiFi.

Q So what do you base your statement on that there's this increase risk of cancer associated with WiFi?

A The fact that the radio frequency radiation is identical to that -- or nearly identical to that from cell phones.

Q So you're basing it on the cell phone studies?

A That's correct.

Q Because, as you've said, the studies haven't been done with respect to WiFi?

A That's correct.

Q And do you believe that your beliefs are consistent with the majority of the scientific community?

MR. MARKHAM: With respect to his last answer?

MS. McKEAN: Correct.

A I think the majority of the scientific community is uninformed on this issue. I think my beliefs are consistent with those individuals that are informed and that are health professionals.

Q So the organizations that disagree with you, do you think that they are not properly informed on this issue?

A Yes.

(Defendant's Exhibit 187 marked)

Q I've handed you what's been marked Exhibit 187, do you see that?

A Yes, I do.

Q And do you see that this is a document from the United States Environmental Protection Agency?

A Yes.

Q Do you see below the title about Nonionizing Radiation From Wireless Technology, do you see that language?

A Yes.

Q And specifically, the third paragraph reads, “At very high levels, RF energy is dangerous.” Do you see that?

A Yes.

Q And then a few sentences in, it says, “Cell phones and wireless networks produce RF, but not at levels that cause significant heating.” Do you see that?

A Yes.

Q Do you agree with that statement by the EPA?

A Yes.

Q Now, the next paragraph states, “Some people are concerned about potential health effects, especially on the developing brains and bodies of children.” Do you see that section?

A Yes.

Q And then it says, “Some studies suggest that heavy long-term use of cell phones could have health effects.” Other studies find any health effects -- I’m sorry, “Other studies don’t find any health effects from cell phone use.” Do you see that?

A Yes.

Q It then says, “Long-term studies on animals exposed to the RF found in wireless networks, Wi-Fi, have, so far, found no health effects.” Do you see that?

A Yes.

Q Do you agree with that statement that long-term studies on animals exposed to the RF found in wireless networks have found no health effects?

A No.

Q You don’t agree with that?

A I don’t agree with that.

Q And why don’t you agree with that?

A Well, there are at least two specific studies that have shown long-term health effects. One by Rapacholli a number of years ago, R-A-P-A-C-H-O-L-L-I, I’m not sure I know how to spell his name, something like that. And then there was a study, I believe last year, from a German group showing elevated cancer in animals exposed to radio frequency radiation for a long period of time. I don’t deny that there are other studies that did not show those effects, but there are some that have. Q: So you disagree with this statement by the EPA with respect to long-term studies?

A Yes.

Q Now --

MR. MARKHAM: Excuse me, you said this is a statement by the EPA?

MS. McKEAN: I said this is -- it comes off the United States Environmental Protection Agency website.

MR. MARKHAM: Well, the first thing below that is “RadTown USA,” I don’t know that to be -- I don’t know what that is.

MS. McKEAN: I can tell you this is on the US EPA website.

Q Do you know what RadTown USA is?

A No.

Q Do you see under the section that says US Federal Communications Commission, FCC, do you see that?

A Yes.

Q Do you see it says, “In the United States, the FCC sets safety guidelines that limit RF exposure.” Do you see that?

[Note: Page 80 missing in original document]

Q But it’s your understanding that those limits are in place today?

A Yes.

(Defendant’s Exhibit 188 marked)

Q I’m handing you what’s been marked as Exhibit 188, do you see that it’s from Health Canada?

A Yes.

Q Have you seen this document before?

A I don’t know, probably have.

Q Okay. Do you see that the first question and answer relates to what Health Canada says about the potential health risk from WiFi, do you see that?

A Yes.

Q And do you see it says, Based on scientific evidence, Health Canada has determined that low level exposure to radio frequency, RF, energy from WiFi equipment is not dangerous to the public. This conclusion is consistent with the findings of other international bodies and regulators.” Do you see that?

A Yes.

Q Do you agree with that statement?

A Absolutely not.

Q So you disagree with Health Canada in their statement with respect to whether low level exposure to RF is dangerous to the public?

A Very much so.

Q And why is that?

A Because they are -- they're not basing their report on scientific evidence. They're basing their report on influence from the industry, been very much involved in the industry since Health Canada, and this is a very divisive ruling and this statement is simply not correct.

Q And they then say, "This conclusion is consistent with the findings of other international bodies and regulators." Do you agree with that?

A Yes.

Q You agree that their finding is consistent with the other bodies?

A Yes.

Q So is it fair to say, then, your opinion differs from that of Health Canada and the other international bodies and regulators?

MR. MARKHAM: Objection. His opinion as to what? Are we talking about 183, are we talking about his opinion about cancer, or what?

Q We just talked a few moments ago about the fact that you disagree with the statement that low level exposure to RF from WiFi equipment is not dangerous to the public, correct?

A Correct.

Q You do disagree with that statement, right?

A I disagree with that statement.

Q You do think there are some dangers?

A I do think there are some dangers.

Q And so your opinion with respect to those dangers differs from that of Health Canada?

A Yes.

Q And is it fair to say that your opinion with respect to the dangers of WiFi also differs with respect to international bodies and regulators?

A Yes, including the FCC.

(Defendant's Exhibit 189 marked)

Q I've handed you what's been marked Exhibit 189, do you see that's from the National Cancer Institute?

A Yes.

Q Are you familiar with the National Cancer Institute?

A Yes.

Q Can you go to the bottom of the first page for me?

A Yes.

Q Do you see the paragraph it states, "The only consistently recognized biological effect of radio frequency energy is heating. The ability of microwave ovens to heat food is one example of this effect of radio frequency energy. Radio frequency exposure from cell phone use does cause heating to the area of the body where a cell phone or other device is held (ear, head, et cetera). However, it is not sufficient to measurably increase body temperature, and there are no other clearly established effects on the body from radio frequency energy." Did I read that correctly?

A Yes.

Q Do you agree with that statement?

A No.

Q Why not?

A Because it's wrong.

Q And can you tell me why it's wrong?

A It's wrong because there's clear evidence that radio frequency exposure at levels that do not cause measurable heating have adverse health effects as documented in my report.

Q And you base that statement on your review of other studies that have been done, correct?

A That's correct.

Q Not on your own studies?

A That's correct.

Q So is it fair to say with respect to that topic, you disagree with the National Cancer Institute?

MR. MARKHAM: Which topic are you talking about?

MS. McKEAN: The one we were just talking about, John.

MR. MARKHAM: Well, I'm sorry, I object to the -- object, vague.

Q Do you recall what we were just talking about?

A Yes, I recall what we were talking about.

Q Specifically, the statement we just read about whether or not use of cell phones, whether it measurably increases body temperature and whether there's clearly established effects on the body from radio frequency energy?

A Well, I disagree with that statement.

Q You disagree with that statement. And is it fair to say your disagreement with that statement also disagrees with the National Cancer Institute?

A Well, if this is an official position of the National Cancer Institute, yes. I'm not sure that it is that, but yes, I disagree with that statement.

Q Can you turn for me in Exhibit 189 to page 5, and there's page numbers on the top right-hand corner, just let me know when you're there?

A Yes.

Q Now, do you see the line about the American Cancer Society?

A Yes.

Q Do you see it states, "The American Cancer Society states that the" -- is it IARC; is that correct?

A IARC, yes.

Q -- "IARC classification means there could be some cancer risk associated with radio frequency energy, but the evidence is not strong enough to be considered causal and needs to be investigated further." Do you see that?

A Yes.

Q Is that your understanding of what the IARC classification means?

A Yes, that's the conclusion that the members of the IARC panel drew.

Q Do you agree with the statement that the -- there was not strong enough evidence to show that there's a cancer risk associated with radio frequency energy to be considered causal?

A No, I do not agree with that. The reason for that classification as possibly carcinogenic, as I believe I mentioned earlier, is the lack of strong evidence in animal studies and the lack of knowledge of the single specific mechanism, but again the reason for the "possibly carcinogenic to humans" was based on the human studies, including some that were supported by WHO that showed elevations, risks of brain cancer in individuals that use cell phones for long periods of time.

Q So is it fair to say that your opinion disagrees with that of the American Cancer Society?

A As evidenced by this paragraph, I don't think my disagreement is great. I think that the IARC classification was unduly conservative, but the IARC panel in that report made clear that there was strong evidence that prolonged intensive use of cell phones increases the risk of brain cancer. In looking at the total body of evidence, considering animal studies, mechanistic studies, the IARC panel concluded it was only the Group 2B, not the Group 2A or Group 1, that that they felt comfortable giving a rating to.

Q Okay. Do you see the statement regarding the FCC on that same page?

A Yes.

Q Specifically, it states that, The FCC, quote, concludes that no scientific evidence establishes a causal link between wireless device use between cancer or other illnesses, end quote. Do you see that?

A Yes.

Q Is that your understanding as to what the FCC has stated with respect to a causal link between wireless devices and illnesses?

A Yes, the FCC has absolutely no human health expertise. It's run by a bunch of engineers and they have no business making

any statement about human health affairs.

Q Is it your understanding that the FCC, in putting together their regulations, did review other studies?

A I have no knowledge of what they reviewed or didn't review.

Q Okay. But it's fair to say you disagree with the statement by the FCC?

A Yes.

Q Do you see the statement on the same page by the FDA?

A Yes.

Q And specifically, it says, "The US Food and Drug Administration notes that studies reporting biological changes associated with radio frequency energy have failed to be replicated and that the majority of human epi" -- help me on that one, epimology (sic/phonetic)?

A Epidemiology.

Q -- Epidology (sic/phonetic) studies --

MR. MARKHAM: Epidemiology.

MS. McKEAN: I think it says -- it doesn't say "demiology," but that's okay.

Q -- "studies have failed to show a relationship between exposure to radio frequency energy from cell phones and health problems." Do you see that?

A Yes.

Q Okay. Is that your understanding as to the FDA's position?

A That's a totally fallacious study -- statement.

Q But is that your understanding as to the FDA's position on this issue?

A Yes.

Q Is it fair to say you disagree with the FDA's position on this issue?

A Strongly.

Q Is it fair to say that you differ with many of the mainstream agencies as to their position as to whether RF coming from wireless networks is dangerous?

A Yes.

(Defendant's Exhibit 190 marked)

Q I've handed you what's been marked as Exhibit 190, do you see that this is a publication from the World Health Organization?

A Yes.

Q And earlier today, I believe you indicated that the World Health Organization is a very credible source, do you remember saying that?

A Yes.

Q Have you seen this statement before?

A No.

Q Do you see on the top it says, "Electromagnetic Fields in Public Health," and it refers to mobile phones?

A Yes.

Q Can you turn to the second page of this document?

A Right.

Q Do you see where it says, "Are there any health effects"?

A Yes.

Q And then it states, "A large number of studies have been performed over the last two decades to assess whether mobile phones pose a potential health risk. To date, no adverse health effects have been established as being caused by mobile phone use." Do you see that?

A Yes.

Q Do you disagree with this statement by the World Health Organization?

A Yes, I do. Their own studies have shown elevations in brain tumors from mobile phone use.

Q Is it fair to say that there are more studies that have shown the opposite?

A No, I don't think it's fair to say. They're sort of equally positive and negative.

Q And do you, in your expert report, look at all of those equally positive and negative studies?

MR. MARKHAM: Objection.

A My expert report is not focused on cancer. My expert report is focused on radio frequency radiation effects on the nervous system, and I certainly consider positive and negative studies, I acknowledge negative studies in my report, and I base my conclusions on the weight of the evidence.

Q So this statement that we're looking at, Exhibit 190, it doesn't mention cancer, correct?

A The whole thing is focused on cancer. They're talking about IARC. It is scientific data that is focusing exclusively on cancer -- oh, maybe not, the third paragraph down does talk about sleep and cognitive function, that sort of thing.

Q So would you agree with me that this doesn't exclusively focus on cancer?

A Yes.

Q And in fact, it relates to all health risks, would you agree with me?

MR. MARKHAM: Objection.

A Yes, I guess that's correct.

Q Okay. Now, on the second page, below "Short-term effects," do you see that section?

A Yes.

Q And do you see the second paragraph below that section?

A Yes.

Q In the middle of the paragraph, it starts, "To date"?

A Yes.

Q Specifically, it says, "To date, research does not suggest any consistent evidence of adverse health effects from exposure to radio frequency fields at levels below those that cause tissue heating. Further, research has not been able to provide support for a causal relationship between exposure to electromagnetic fields and self-reported symptoms, or electromagnetic hypersensitivity." Do you see that?

A Yes.

Q Now you're testifying in this case that electrohypersensitivity does exist, correct?

A Yes.

Q And would you agree with me, at least with respect to this statement that we're looking at on Exhibit 190, that the World Health Organization seems to disagree with you?

A Yes.

Q Is it your understanding that the World Health Organization does disagree with you with respect to whether or not EHS exists?

A Yes.

Q Is it your understanding that the World Health Organization's position is that there has not been sufficient research that establishes a causal relationship between exposure to EMF and the diagnosis of EHS?

A That is their position and I strongly disagree with it.

Q And that's despite the fact that earlier today you told me that the World Health Organization is a very credible source, correct?

A Yes.

Q And does the World Health Organization -- strike that. Are scientists part of the World Health Organization?

A Yes, and nonscientists, also.

Q And earlier today, you talked about the FCC not being scientists; is that correct?

A Not being health professionals.

Q Okay. Does the World Health Organization have health professionals on its staff?

A Yes, it does.

MS. McKEAN: Can I have this marked, please.

A -- But I should say in regard to that, that the World Health Organization's Nonionizing Radiation Committee has been dominated by non-health professionals, by engineering people that have basically denied any health effect of nonionizing radiation below the intensities that cause tissue heating.

Q Do you have any knowledge that those individuals you spoke about have tried to quiet the opinions of others on the World Health Organization boards?

A Yes, but it would be difficult for me to provide documentation. The former Chair of the Nonionizing Radiation Committee of the World Health Organization left and immediately was employed by a mobile phone company in Italy. The current woman that Chairs the panel has some background in epidemiology, but also has strong ties to the cell phone industry. So, there are conflicts of interest. The World Health Organization is like any other organization. It's composed of people, people that have various backgrounds, have various prejudices, and I do not consider their statements to be an objective statement reflecting the body of evidence on a variety of health effects specifically, electrohypersensitivity.

Q And you think that your review of the materials has been objective?

A Yes.

Q Where the World Health Organization's review has not been objective?

A Yes.

Q And is your belief on that point a mainstream belief in the scientific community?

A It's hard to say what's mainstream. I think I'm more informed than most people, and I think there are many informed people that are in agreement with my belief. The majority of the health professionals are not very well informed on this issue. So the mainstream view of the informed people, I think, is consistent, but a lot of people don't know anything about EHS.

Q Do you have any idea what led to the World Health Organization making this statement about the lack of research to support a finding of EHS in October of 2014?

A No, I don't. They obviously didn't read my papers.

MS. McKEAN: Can I have this marked, please.

(Defendant's Exhibit 191 marked)

[Note: Pages 96-97 missing in original document]

with wireless technologies, including high speed internet access?

MR. MARKHAM: Well, I'd like him -- if you're going to be asking him about these things we haven't looked at, I'd like you to read through that thing carefully before you make any more comments about the little snippets that she's asking about in each of these documents. So read the whole thing.

MS. McKEAN: Feel free to do so.

(DEPONENT PERUSING DOCUMENT)

THE DEPONENT: All right.

Q So, did you see in there that the World Health Organization indicates that EMF has not been shown to be a cause of electromagnetic hypersensitivity?

A Yes, I did, but this is dated from what year?

Q I believe it has the date on the front of --

A It says prior to the release of the IARC report.

Q Okay. But do you see that it says that?

A Yes.

Q And we saw a few moments ago that a very similar statement was made in the World Health Organization's fact sheet in October of 2014, correct?

A Correct, they're both wrong.

Q You disagree with both statements?

A Yes, absolutely.

Q Can you turn for me to the third page of Exhibit 191?

A Yes.

Q There's Protection Standards listed there, do you see that?

A Yes.

Q Earlier today, we talked about the FCC standards, correct?

A Yes.

Q And you indicated you understood what those were?

A Correct.

Q And you disagreed with those standards?

A Yes.

Q Now, there's some other standards mentioned in this Exhibit, correct?

A Yes.

Q Specifically, there's some standards from the International Commission on Nonionizing Radiation Protection, do you see that?

A Yes.

Q Do you know what that is?

A Yes.

Q What is that?

A It's a private organization that has self-appointed members that's dominated by physicists and engineers. It has no legal standing, but it is commonly acknowledged as having set standards.

Q And does the mainstream scientific community usually rely on the standards put out by that Commission?

MR. MARKHAM: Objection, vague.

A Their standards are commonly quoted, yes.

Q Is it fair to say their standards are commonly relied upon?

MR. MARKHAM: Objection, by whom? Vague.

MS. McKEAN: You can still answer the question.

MR. MARKHAM: Same objection.

A They're relied on by some organizations and some individuals. They're not relied on by others.

Q Is it fair to say that the standards of the International Commission on Nonionizing Radiation Protection are similar to the FCC's standards that we talked about earlier today?

A Yes, they are.

Q Do you have an understanding that the -- that Commission, which I see some abbreviations here, so I'm going to use that Commission -- those abbreviations, specifically, ICNIRP?

A ICNIRP.

Q What is it?

A ICNIRP.

Q ICNIRP, okay. Do you have an understanding that ICNIRP revised their guidelines in 2009?

A I don't recall the year, but they did revise their guidelines somewhat.

Q Okay. And is it fair to say that those guidelines are still consistent with the FCC guidelines that we talked about earlier today?

A Yes.

Q I also see some guidelines from the Institute of Electrical and Electronic Engineers, correct?

A Correct.

Q And I believe that's IEEE, correct?

A Yes.

Q See, that one I know. Can you tell me what the IEEE is?

A It's an organization of electrical and electronic engineers.

Q Are you a member of IEEE?

A I certainly am not. They have no health expertise whatsoever.

Q Are their standards consistent with the FCC's guidelines that we talked about earlier today?

A Yes, they are. All of the agencies that are dominated by engineers and physicists deny any adverse health effect that's not caused by tissue heating, and they all totally ignore the enormous body of evidence that shows that there are biological effects and adverse health effects at much lower intensities of exposure.

Q So is it fair to say that you do not agree with IEEE with respect to the standards they put out?

A I certainty do not.

Q And you don't agree with --

A I don't think they have any basis for making standards on health effects when they have no health expertise.

Q Do you know if they bring in health expertise when they are considering changing standards?

A They will probably bring in individuals that will buy their standards. I don't have -- I shouldn't answer that, I don't have any knowledge of what they -- how they bring in people for making decisions.

Q So I believe you said earlier you don't have any knowledge as to how the FCC goes about coming up with their standards, correct?

A No, I don't think I said I have no knowledge. I have visited with the FCC and advocated for them to revisit their standards. I was told by the FCC people that they're not a health agency, that they have no health expertise, and basically, they left it there, so yes, I know that they review standards every now and then, but how can you make standards based on health effects when you have no health expertise and when you have individuals with health expertise offering to assist them, and they don't make any effort to utilize that expertise.

Q The conversation you just mentioned, when did that occur?

A Maybe 3 years ago, 4 years ago.

Q So other than that conversation -- actually, how long was that conversation?

A It was the whole morning.

Q Other than that conversation, do you have any other knowledge as to how the FCC comes up with its standards?

A None that I can quote you specifically, I mean, I've read many documents that have reviewed FCC policy, I don't recall specifically in there statements about how they developed their standards.

Q Do you know whether or not the FCC brought in health professionals to weigh in when deciding whether or not to change

their standards?

A I don't know whether they brought in people, I know that they have no internal health expertise.

Q How about ICNIRP, do you know if they brought in health professionals when they considered what the appropriate standards were?

A No, I don't know.

Q Do you know if the IEEE brought in health professionals when they considered what the appropriate standards for RF exposures were?

A No.

Q Are there any jurisdictions that have adopted your suggested limit from the BioInitiative Report?

A Jurisdictions in terms of countries, I don't think so, but the standards for radio frequency exposure in many countries are not much higher than our recommendations, that's true for Poland, for Israel, for Russia, I had a slide on this yesterday, but I don't recall others, and then there are other countries that have very much lower standards than ICNIRP, Canada, US, but still above the standard that we recommended in -- the precautionary level we recommended in the BioInitiative Report.

Q What are those countries that have lower standards?

A Well, I mentioned Russia, Poland, Israel. I believe Belgium is one. The BioInitiative Report contains all of that information, what the standards are in different countries, I don't recall all of the details right now.

(MR. MARKHAM LEFT ROOM)

Q Is it fair to say that the BioInitiative Report has been highly criticized by the mainstream scientific community?

A Yes.

Q And was the Health Council of the Netherlands one of the agencies that criticized the BioInitiative Report?

A Yes.

Q Do you remember why the Health Council of the Netherlands criticized the BioInitiative Report?

A Well, primarily, because we told them that they were wrong.

MS. McKEAN: Can I have this marked, please.

(Defendant's Exhibit 192 marked)

Q I've handed you what's been marked as Exhibit 192. This is a report from the Health Council of the Netherlands, do you see that?

A Yes.

Q Have you seen this before?

[Note: Pages 106-109 missing in original document]

A -- And I strongly disagree with that statement that it's not an objective view. It was an encyclopedic review, including of

negative studies, but it certainly drew different conclusions than those from ICNIRP and the other national and international organizations.

Q Did it review all other studies that had found opposite to what you were advocating for?

A Absolutely. Do you know the number of references in that BioInitiative Report, like, what, 5-or-6,000, including positive and negative studies, but it didn't dismiss the positive studies in the way that the other agencies have done.

Q So you disagree with this critique of the BioInitiative Report put out by the Health Council of the Netherlands?

A Strongly.

Q Now, the Health Council of the Netherlands was not the only group to greatly criticize the BioInitiative Report, correct?

A Correct.

Q The Ministry of Health of New Zealand, was that another group that greatly criticized the BioInitiative Report?

A I don't recall, it may well have been. We got under the skin of a number of health organizations.

MS. McKEAN: Can I have this marked, please.

(Defendant's Exhibit 193 marked)

Q I just handed you Exhibit 193, but before we look at that, I just have one more question on Exhibit 192. Exhibit 192 was put out by the Health Council of the Netherlands, correct?

A Yes.

Q And that involved health professionals, correct?

A I have no knowledge of who that involved.

Q Now, I've handed you what's been marked as Exhibit 193, this is a report entitled, "Health Effects of Non-ionising Fields," do you see that?

A Yes.

Q And it seems to be put out by the Ministry of Health of New Zealand, do you agree with me there?

A That's what it says.

Q Are you familiar with that organization?

A No.

Q Are you aware that it contains health professionals?

A Nope.

Q Can you turn for me, please, to page 16, the number's on the bottom left. Do you see the section entitled, "Recent Overseas Reviews"?

A Right.

Q Do you see the paragraph that starts, "The BioInitiative Report"?

A Right.

Q And specifically, it states, "The BioInitiative Report, first published in 2007 and partially updated in 2012 and 2014, is sometimes cited by people concerned about the possible health effects of exposure to RF fields. The Committee finds that this report has weaknesses that undermine its credibility and conclusions and does not place any weight on its findings or recommendations." Do you see that?

A Yes.

Q Were you aware that that statement was made?

A I've never seen this report, I know nothing about it.

Q Okay. You see it then references an Appendix E?

A Yes.

Q Can you turn for me to Appendix E, which is page 45 of the report. Are you there?

A Yes.

Q Now, it indicates in the second sentence that the stated intention of the BioInitiative Report was to quote, To document the reasons why current public exposure standards for nonionizing electromagnetic radiation are no longer good enough to protect public health, end quote. Do you see that?

A Yes.

Q Was that the purpose of the BioInitiative Report?

A Yes, it was.

Q Now, it then goes on to detail weaknesses which undermine the BioInitiative Report's credibility, do you see that?

A Yes.

Q And it states, "The stated objective of using the publications cited to support a particular point of view" as one of the weaknesses, do you see that?

A Yes.

Q Do you agree with that statement?

A Absolutely not.

Q It indicates that a systematic review of publications was not completed?

A That is totally wrong and totally false. This was a very systematic review and encyclopedic in its review of publications both positive and negative with critiques of the negative publications, and of the positive, demonstrating weaknesses and strengths of both.

Q Now, you didn't perform any of those reviews, though, correct?

A I did, I certainly -- well, my contribution was the Public Health Chapter, which was based on the health effects literature, so, yes, I did perform those reviews, .6 but limiting my contribution to primarily the human studies.

Q So how do you know that the other authors conducted a systematic review of publications?

A Well, I obviously read their chapters and have seen their bibliographies, which are very, very extensive.

Q But you'd agree with me that the Ministry of Health of New Zealand did not. think that such a systematic review had been completed?

A Well, they can think what they want, but they were wrong if they didn't think we did a systematic review.

Q Now, the next criticism says, "the conclusions were not a consensus view of the chapter authors, some of whom disagreed with the conclusion. Do you see that?

A Yes.

Q Do you agree with that statement?

A I have no - I don't understand where that statement came from, I know of no disagreement among the .authors on the conclusions of the BioInitiative Report. There was some controversy in the 2012 version on the lowering of the standards, and I was one of the people that thought that was perhaps not wise, but there was no major disagreement among the authors, to my knowledge, in the 2007 report.

Q Okay. Now, you see that this report is dated 2015?

A Yes.

Q So this would have been after the. 2012 update?

A Yes.

Q You see another criticism is "the selective use of data with little or no mention of the reports that do not support the conclusions"?

A It's totally false.

Q So you disagree with that-statement?

A I totally disagree.

Q Okay. And you then see it says "no rationale being presented for the very low RF exposure limits proposed"?

A And again, that's totally wrong, there's detailed justification, which is based on -- in the 2007 report, the available literature primarily on both animal and human cellular studies, in 2012, that lower value was primarily based on cellular and animal studies for which there was little support in human epidemiological studies.

Q Okay. Now, you, yourself, said though that these were not guidelines, rather they were goals, correct?

A That's correct.

Q And you also said that they are difficult to obtain?

A That's right. But again, the point was to show that the current standards that the FCC, ICNIRP and all these other organizations that deny any adverse health effect at intensities that don't cause tissue heating are just inadequate. We were not recommending those as standards, that would have been unrealistic and caused more problem than it would solve, but as goals, they're appropriate.

Q So why propose a number at all then?

A Well, we asked that question among ourselves and we talked about that a long time. To say that they're inadequate without giving some indication of what would be an appropriate goal seemed not very -- or it just wasn't sufficient, and so again, we didn't want to be proposing things as standards, but we wanted to give some indication of a level for which there was minimal evidence for adverse health effects below that level. As I said earlier, for cancer, a carcinogen, the EPA standard is that there is no level of a carcinogen that doesn't increase cancer. It's just that it's such a low elevation and risk, probably not very important for society in general.

Q Can you turn for me to page 46 of Exhibit 193, specifically, to the discussion about Electrohypersensitivity. Do you see that section?

A Right.

Q Now, this is a further critique of the BioInitiative Report, correct? 9. A Yes.

Q And it indicates that EHS is covered in several sections of the BioInitiative Report, correct?

A Yes.

Q And --

MR. MARKHAM: Excuse me, I want him to read this all the way through, the provision on electrohypersensitivity, and maybe this is a good time to take a lunch break.

MS. McKEAN: I'd like to finish my questions on this before we take a lunch break.

MR. MARKHAM: All right, well, then, I'd like him to read through it very carefully. You're now asking questions about this case, as opposed to the general world, in my opinion. So, I'd like him to read through the portion of this report dealing with that so that he can answer it in the context of the whole report, not just a line or two.

MS. McKEAN: What I would prefer to do, John, is ask him my question, and then he can read whatever he wants to answer that question.

MR. MARKHAM: Fine. What's your question?

Q Okay. So, you see it references the Public Health Policy Recommendations section of the BioInitiative Report?

A Yes.

Q Is that the section that you wrote?

A Yes.

Q Okay. So, this seems to refer to the section that you wrote in the BioInitiative Report?

MR. MARKHAM: Just asked and answered, but you can go ahead and say yes again.

A Yes.

Q Okay. And specifically, it says Section 24, is that the section you wrote?

A It was 24 in the 2007, yes, it wasn't revised in 2012.

Q Now, it states that in that section, you discuss two reviews of Johansson, which conclude that EHS symptoms are caused by EMF's, but you don't mention other reviews by Rubin in 2005, 2010, and 2011, which conclude the opposite, do you see that?

A Yes.

Q Did you fail to mention the reports that found opposite?

MR. MARKHAM: Objection. I want him to read through as much of this as he needs to before you start asking your questions on one page -- one sentence in a 45 page report.

MS. McKEAN: Okay, I'm asking him, though, John, he mentioned -- he can read it if he needs to --

MR. MARKHAM: Well, that's what I'm saying.

MS. McKEAN: -- Except I'm asking him about the BioInitiative Report and whether or not he failed to mention or failed to review other reviews when referencing a findings in Johansson.

MR. MARKHAM: Can I say something now? You said that you would read the question and he could read what he wants to read. So, I just interjected after you read the question in your high cadence expected answer right away that he is now allowed to read what he wants to read before he answers your question, that's where we are.

Q Dr. Carpenter, I want to be clear, if you need to read more of this, you can feel free to do so.

THE DEPONENT: I need to see the Chapter 24 in the BioInitiative Report, do you have that here?

MS. McKEAN: I don't have it here. If we need to go back to this, I could pull it out.

MR. MARKHAM: Well, that's his answer.

A I can't answer this question. Let me just explain a little bit. The chapter that was relevant to EHS was written by Johansson. The Chapter 24 was a summary chapter, so I don't have any problem if the Rubin reviews, and those are reviews, was not mentioned in Chapter 24, I would be concerned if they weren't in the expanded version that Johansson wrote for the BioInitiative Report.

Q Did you rely upon the Johansson report at all in preparing your expert report in connection with this case?

A No.

Q Did you review the sixteen papers reviewed by Rubin in preparing your expert report in connection with this case?

A I can't swear that I looked at all sixteen, but I certainly looked at the great majority of them, and all of the Rubin papers, yes.

Q Is it fair to say that Rubin has consistently found that there is not objective evidence of EHS?

A That's correct.

Q And is it fair to say you disagree with those papers by Rubin?

A I think there's some major weaknesses in those papers. The exposures that he used, if I remember correctly, were 50 minute exposures, not all day at school, and again, if I recall correctly, he followed people for symptoms for a period of less than one hour. The -- I don't think that -- now, most of Rubin's papers are reviews of everybody's work, not experimental papers of his own, some are experimental, but they're just limitations to the studies, I don't think that -- I certainly acknowledge those studies in my review of electrohypersensitivity, and I am surprised if I didn't at least mention one of the Rubin papers in Chapter 24, but certainly, they are discussed in detail in the Johansson report, I'm confident.

Q Now, this document mentions the failure to consider the nocebo effect in the BioInitiative Report, do you know if that was considered in the BioInitiative Report?

A I don't know if that word was used. Again, it's been a long time, so I don't really recall.

Q Did you consider the nocebo effect in preparing your expert report in this case?

A I certainly am aware of the nocebo report. If you look at my report, my report is focused entirely on effects of radio frequency fields on brain physiology and metabolism. It's not focused -- I mean, I acknowledged Rubin, I acknowledged, Eltiti (phonetic), or whatever the name is, their reviews, but the report is based on documented effects by credible researchers and first rate scientific journals that show that radio frequency fields effect brain physiology and brain metabolism. So, the nocebo effect is irrelevant to my report and I expect will be irrelevant to what I'm asked to testify about at trial.

Q In addition to --

MR. MARKHAM: If we're going to a new document, I want to break for lunch, it's 1:00.

MS. McKEAN: I'd like to finish this topic.

MR. MARKHAM: No, we don't -- it's 1:00, I think the witness would like a break, we would like to have lunch. This topic, what topic? The topic is EHS, I hope we'll get there sometime.

MS. McKEAN: John, you've missed some of the topics, because you've stepped out for phone calls, so don't tell me we haven't covered that. Fine, John, we'll take a break, even though I think in 5 minutes I could have covered the topic I wanted to finish with, but that's fine.

MR. MARKHAM: What difference does it make

[Note: Pages 123-126 missing in original document]

to?

MR. MARKHAM: Well, first of, all you can count on my word without having just said that, but beyond that, I believe under the Rule, if I've designated him for the things in Paragraphs 2, 3 and 4, I can't surprise you in trial and say, Oh, by the way 5, 6 or 7, so you're covered, and I hope that focuses the inquiry, but it's your deposition, but you can rely on it, yes.

Q So with respect to your opinion that exposure to EMF's can cause EHS, can you tell me what level of exposure to EMF has been shown to cause EHS?

A Well, I can't give you a microwatts per centimeter squared number. The issue is that individuals vary greatly in sensitivity, and only a very small minority of people have EHS, or at least that they recognize. I mean, my wife used to sit by the WiFi router and she kept complaining of ringing in her ears, and I told her she had EHS, and she told me I was crazy, but then she moved the router and she no longer had ringing in her ears. So, you know, it's a degree thing. Some people are significantly disabled by exposure to radio frequency fields. Most people are not. George is one of those people that is significantly disabled.

[Note: Page 128 missing in original document]

here today --

MR. MARKHAM: Well, I think your questions are allowing him to stray. I think this morning may have been interesting for you, and I think I know how you're going to try to use it, but really, I have testified -- I have stipulated to what he's going to give opinions on. That's what he's here for. He's not going to say G[Text redacted in copy.] is disabled. The Judge is going to say whether or not he's disabled under the law based upon the opinions that he gets. We have people who are going to testify that these particular types of symptoms can cause disabilities under the Act, but not this witness.

MS. McKEAN: Okay. Thank you, I appreciate that -- that clarification, that is.

Q So back to my initial question, which was regarding the levels causing the symptoms, I believe you said you can't give an exact microwatts per centimeter figure, correct?

A That's correct.

Q Can you give me a general range as to what the studies have found?

A No, I can't even do that. The thing is that individuals vary so greatly, that intensities that most of

[Note: Pages 130-135 missing in original document]

A I think what I'm saying, it's my expert opinion that it's more likely than not that G[Text redacted in copy.] has EHS.

Q Even though you know nothing about the school environment?

A I don't know anything about the school environment -- actually, that's not true, I know about the school environment from the reports I've read, both from the two engineering people --

MR. MARKHAM: Really, I have to object. I've told you, he's not going to testify about G[Text redacted in copy.] having EHS. I've stipulated to that. What's a stipulation worth doing if you keep ignoring it?

MS. McKEAN: Well, I just --

MR. MARKHAM: He's going to testify --

MS. McKEAN: Can you also stipulate that if the witness starts to testify about this at a hearing or at the trial, that you will agree that that's beyond the scope of his expertise and that he will be stopped?

MR. MARKHAM: If I make the stipulation four times, will that work for you, as opposed to three or two or one?

MS. McKEAN: This is a little bit different.

MR. MARKHAM: No, this is not a little bit different. This witness is being offered to testify

[Note: Pages 137-142 missing in original document]

Q Okay. You said a few moments ago that you felt that the exercise of going through and identifying which of these related to WiFi would not be a helpful exercise, because you felt the exposure levels in these studies were similar; is that correct?

A Not the exposure levels, that the nature of the radio frequency radiation is more or less the same. There are some differences, for example, smart meters have much more pulses than WiFi, although WiFi has pulses as well. But, I think one thing that I feel very strongly, and I think is supported by the literature, is that it's the intensity of the radio frequency

radiation, not whether it comes from WiFi or from a cell phone, from a cell tower, from a smart meter, it's the intensity and the duration of exposure that are the critical variables in EHS.

Q And do you have a particular intensity level that you designate as safe versus non-safe?

A Well, I would only have to go back to that precautionary level from the BioInitiative Report. I think the short answer to your question, though, is no, I don't have -- I think when you have an exposure at whatever level that triggers symptoms in a person, then that exceeds the safety level, but that intensity of exposure is going to vary greatly from individual to individual.

Q The duration of exposure you mentioned, do you have a particular timeline that you -- time limit that you put on that?

A Well, I can comment on the timeline. For example, all of the studies of the Defendant's expert, Eltiti, are for 15 minute exposure, grossly inadequate. George was at school for 6 hours a day and his symptoms often didn't develop until he had been at school for a significant period of time. Now, the symptoms also lasted for various periods of time. The provocation studies that have been done --in the Rubin studies, his exposure was for, I think, 50 minutes, and then he followed people for 50 minutes, and then called them the next day to see if they had headaches. It's very difficult to do those experiments, I understand that, but a 15 minute exposure is grossly inadequate, and not related to the real world exposure that a kid would get in school or that another person would get just in their daily life when they're in elevated RF environments for prolonged periods of time.

Q Now, if a child had EHS, would you expect them to come to school exhibiting the symptoms?

A No, I would not. I would expect the symptoms to develop after some latency. It would be, of course, very dependent on the degree of their electrohypersensitivity,

[Note: Pages 145-191 missing in original document]

case that we're here for today, right?

A Yes.

Q Okay. Can you list a case for me where your testimony about EMF's has been accepted as persuasive?

A No.

MS. McKEAN: Now's a good time for a break.

(BRIEF RECESS)

(Defendant's Exhibit 203 marked)

Q Dr. Carpenter, could you please turn back to your report, Exhibit 183, for me, please?

A Yes.

Q In your report, you mention the Hill Criteria?

A Yes.

Q Can you tell me what that is?

A Well, the Hill Criteria are a series of issues on which one -- Hill proposed them as considerations when you're looking to establish causation, and depending on different people as they review that paper, there's something like 7 to 11, and Hill, specifically, did not set these up as absolute standards, but rather as factors that should be considered, and they include things

like strength of the evidence, coherence, biological plausibility, dose response curve. I'm forgetting some others, but it's a series of things that are appropriately considered.

End of Document

CARPENTER DEPO EXHIBIT 20

DAVID O. CARPENTER, M.D.

PREVIOUS DEPOSITIONS AND TESTIMONY

Jordon vs. Georgia Power and Oglethorpe Power, deposed and testified at trial for the plaintiff in 1995.

Jahan-Parwar vs New York State, deposed for the defendant, 1996

Abernathy vs. Monsanto, deposed for the plaintiff, 1998

Bermuda Digital Communications vs. Westend Properties, testified for the plaintiff, 2000.

Owens vs. Monsanto, deposed for the plaintiff, 2001.

Owens vs. Monsanto, testified for the plaintiff, 2001.

Abernathy vs. Monsanto, testified for the plaintiff, 2001

Riverkeeper vs. Atlantic Richfield Company, deposed for the plaintiff, 2001.

Antonia Tolbert et al. vs. Monsanto Company, Pharmacia Corp., and Solutia Inc., deposed for the plaintiffs, 21-22 January 2003. Mark Englehart, Attorney 334-269-2343.

Aaron et al. vs. Chicago Housing Authority et al., deposed for the plaintiffs, 5-6 March 2003.

Kellum et al., vs. Kuhlman Corporation, deposed for the plaintiffs, 4 September 2004. Doublas Mercier, Attorney, 601-914-2882.

Allgood et al. vs. General Motors Corporation, deposed for the plaintiffs, 8-10 December 2004. Brian J. Leinbach, Attorney. 310-552-3800.

Maggie T. Williams et al. vs. Kuhlman Corporation, deposed for the plaintiffs, 1 February and 25 February 2005. Douglas Mercier, Attorney, 601-914-2882.

Solutia Inc. et al., Debtors, vs. Monsanto Company and Pharmacia Corporation; deposed for the plaintiffs, 12 September 2006. Samuel E. Stubbs, Attorney; 713-425-7345.

Charles W. Adams, et al., vs. Cooper Industries, Inc. et al., deposed for the plaintiffs, 28-29 September 2006. Donna Keene Holt, Attorney. 865-212-3294.

Arthur D. Dyer et al. vs. Waste Management et al., deposed for the plaintiffs, 2 November 2006. Mark L. Thomsen, Attorney. Cannon & Dunply, Brookfield, WI 53008.

Clopten et al. vs. Monsanto, deposed for the plaintiffs, 31 January 2007. Robert Roden, Attorney. 406-525-2665.

Marty Paulson et al. vs. Monsanto, deposed for the plaintiffs, 7 August 2007. Torger Oaas, Attorney. 406-525-2665.

John Edward Martinez and Gladys Yolanda Martinez vs. Entergy Corporation et al., deposed for the plaintiffs, 16 April 2008. Julie Jacobs, Attorney. 504-566-1704.

Fannie Wayne et al. vs. Pharmacia Corporation, et al., deposed for the plaintiffs, 29 October 2008. John E. Norris, Attorney. 205-541-7759.

Fannie Wayne et al. vs. Pharmacia Corporation et al., testified for the plaintiffs, 31 March-1 April, 2009. John E. Norris, Attorney. 205-541-7759.

Clement Passariello, et al., vs. CL&P, et al.; William Korzon, et al., vs. CL&P, et al.; Louis Gherlone et al., vs. CL&P, et al.; and William Ho, et al., vs. CL&P et al., deposed for the plaintiffs, 13 April 2009. Benson A. Snaider, Attorney. 203-777-6426.

Before the Pennsylvania Public Utility Commission, docket No A-2009-2082652, et al. Testified on behalf of the Saw Creek Estates Community Association, 2 September 2009. Paul M. Schmidt, Attorney. 215-569-2800 x161.

James Alford et al. v. Kuhlman Corporation, et al., pending in the USDC, Southern District of Mississippi, Deposed for plaintiffs, 20 August 2009. Shiela Bossier, Attorney. 601-352-5450

Fannie Wayne et al. v. Pharmacia Corporation. Deposed for plaintiffs, 23 September 2009, Timothy C. Davis, Attorney. 205-327-9115.

Before the Minnesota Public Utilities Commission in the matter of the route permit application by Great river energy and Xcel Energy for a 345 kV transmission line from Brookings County, South Dakota to Hampton, Minnesota. Testified for plaintiffs, 16 December 2009. Paula Maccabee, Attorney. 651-775-7128.

Highland Lakes Estates et al.v. Republic Services of Florida et al., Deposed for the plaintiffs, 23 April 2010. John W. Frost II, Attorney. 863-533-8985.

Zina G. Bibb, et al. v Monsanto Company et al. Deposed for plaintiffs, 28 April 2010. W. Stuart Calwell, Attorney, 304-343-4323.

Highland Lakes Estates et al., v. Republic Services of Florida et al., Testified for the plaintiffs, 13 May 2010.

Nora Williams, et al., v. City of Jacksonville, et al. Deposed for the plaintiffs.15 July 2010. Samuel W. Wethern, Attorney.

Ronald Cybart et al., Michael Campanelli, and Donald and Theresa Shea, et al.v. CL&P. Deposed for the plaintiffs. 15 July 2011. Benson A. Snaider, Attorney.

Maria Snoops vs. Lyon Associates, Inc. and Insurance Co of the state of Pennsylvania. Deposed for the plaintiff, 1 November 2011. Matthew J. Witteman, Attorney. 415-363-3106.

John Edward Martinez and Gladys Yolanda Martinez v. Entergy Corporation, et al., Deposed for the plaintiff, 19 December 2011. J. Patrick Connick, Attorney. 504-347-4535.

AHM and David Mark Morrison vs. Portland Public Schools. Deposed for the plaintiffs, 25 January 2012. Shawn E. Abrell, Attorney. 503-224-3018.

Judy Prescott Barnett v Robert E. Carberry et al. Deposed for the plaintiff, 6 April 2012. Whitney North Seymour, Attorney . 212 455-7640.

Association Quebecoise de Lutte Contre La Pollution Atmospherique et al. vs. Hydro Quebec, et al. Testified for the plaintiffs, 17-18 May 2012. Domineque Neuman, Attorney. 514-849-4007.

Harold Barker et al. vs. East Kentucky Power Cooperative, Case No 2013-00291, Testified

FortisBC vs Citizens for Safe Technology. Testified for the plaintiff, 15 March 2013. David M. Aaron, Attorney. 250-551-6840.

John Edward Martinez and Gladys Yolanda Martinez v. Entergy Corporation et al., Deposed for the plaintiff, 21 June 2013. J. Patrick Connick, Attorney. 504-347-4535.

Village of Stillwater et al. and Saratoga County Water Authority v. General Electric Company. Deposed for the plaintiff, 10 April 2014. Donald Boyajian, Attorney. 518-463-7784.

Ron Plain and Ada Lockridge v. Director, Ministry of the Environment et al., Deposed for the plaintiff, 13-14 May 2014. Margot Ventor, Attorney, 604-685-5618.

Harry Naeole vs. Alaska Barge & Transport, Employers, Continental Insurance Company/CAN, Carrier. Deposed for the plaintiff, 27 May 2014. Matthew Witteman, Attorney, 415-362-3106.

Case No U-17767. Before the Michigan Public Service Commission in the matter of the application and request of the Detroit Edison Company seeking approval and authority to implement its proposed Advanced Metering Infrastructure opt out program. Testified to the Commission. Case No. U-177667; July 2015

Graff et al. v. Haverhill North Coke Company et al., Deposed for the plaintiffs, 30 October 2015. D. David Altman, Attorney. 513-721-2180

Edwin Spirer et al. v. Monsanto Company, et al., Deposed for the plaintiffs, 17-18 December 2015. Allan Stewart, Attorney.

Roslyn Dauber and John DiCostanzo vs. Monsanto Company et al. Deposed for the plaintiffs, 12 February 2016. Allan Stewart, Attorney.

America Unites for Kids, et al. v. Sandra Lyon et al. Deposed for the plaintiffs, 1 March 2016. Charles Avrith, Attorney 310-473-1200

Roslyn Dauber and John DiCostanzo v. Monsanto Company et al. Testified for the plaintiffs, 15 -16 March 2016. Allan Stewart, Attorney.

Fred Steele and Arutyun Karabadzhakyan vs. Monsanto. Deposed for the plaintiffs, 30 March 2016. Allan Stewart, Attorney.

Fred Steele and Arutyun Karabadzhakyan vs. Monsanto. Testified for the plaintiffs, 19 April 2016. Allan Stewart, Attorney.

Benito Walker et al., vs. Monsanto. Deposed for the plaintiffs. 25 April 2016. Steven Kherkher, Attorney

G, a 12-year old minor suing by a fictitious name for privacy reasons, Mother and Father v. The Fay School. Deposed for the plaintiffs, 23 May 2016. John Markham, Attorney

Edwin Spirer et al. v. Monsanto Company et al. Deposed for the plaintiffs, 4 August 2016. Steven Kherkher, Attorney.

In the Matter of the Petition of Jersey Central Power & Light Company Pursant to N.J.S.A. 40:55D-19 for a Determination that the Mommouth Count Reliability Project is Reasonably Necessary for the Service, Convenience or Welfare of the Public, BPU Docket No. EO16080750. Testified for the plaintiffs, 11 April 2017, Peter Dickson, Attorney.

Before the Pennsylvania Utility Commission, Docket No.C-2017-2620710 Richard N Myers v PPL Electric Utilities Corporation. Testified for the plaintiff, 2 April 2018.

G.C and J.C. by their next friend and mother, Angela Tsiang, Plaintiffs, vs. South Washington County School District 833, and Dr. Keith Jacobus, Superintendent of the South Washington County School 833. Deposed for the plaintiffs, 6 July 2018.

James Sampson et al. v. SunCoke Energy, Inc., et al. Testified for the plaintiffs. 10 September 2018.

City of Spokane, a municipal corporation, located in the County of Spokane, State of Washington vs. Monsanto Company, et al. Deposed for the plaintiff, 12 December 2019.

Kerry L. Erickson et al. vs. Monsanto Company, et al. Deposed for the plaintiffs, 18 June 2020.

Emilio. M. Kosrovani, a single individual, vs. Minor &James Professional Limited Liability Company et al., Deposed for the plaintiff, 14 August 2020

Angela M. Bard, et al., vs. Monsanto Company, et al. Deposed for the plaintiff, 6 January 2021.

Kerry L. Erickson et al. vs. Monsanto et al. Deposed for the plaintiffs, 14 January 2021.

Kerry L. Erickson et al. vs. Monsanto et al.. Testified for the plaintiffs, 24 and 28 June 2021.

Angela M Bard, et al. vs. Monsanto et al., Deposed for the plaintiffs, 1 September 2021.

Angela M Bard, et al. vs. Monsanto et al., Testified for the plaintiffs, 30 September 2021.

Deepwater Horizon CELO Cases, US District Court, Northern District of Florida, Civil Action No 3.19-cv-00963-MCR-GRU, Deposed for the plaintiffs, 9 December 2021.

CARPENTER DEPO
EXHIBIT 21

Carpenter, David O

From: Ed Friedman <edfomb@comcast.net>
Sent: Wednesday, March 20, 2013 2:49 PM
To: Carpenter, David O
Subject: FW: Carpenter DR Repsonses
Attachments: Notes on AGNIR & IEGMP Stewart Group formed in 1999 and issued report in May.docx; 2000 Stewart Rpt Scientific Evidence.pdf

David,

Comments, references and attachments from Dianne [except 001 which I just wrote]. EXM Questions are at bottom of email.
Thanks-Ed

EXM-017-001...While there are plenty of accounts of electrical sensitivities from exposure to a wide variety of RF sources, there is something unique to smart meters that has triggered an often rapid response in individuals with no prior sensitivities and caused a worsening of symptoms for many with pre-existing sensitivities [see Conrad survey]. Possible reasons for this could include very high micro bursts of voltage, additive impact of an RF source or power quality [dirty electricity] issues getting into the home wiring to name a few. The evidence of a blind adverse response for some segment of the population is without question. People around the world are having similar reactions to smart meter exposure. While the mechanism may be unknown, that is no excuse not to deal promptly with the problem in a manner protective of public health.

EXM-017-002....since the WHO 2-B classification was f**or all of RF from any source**...then that would include smart meters.....and they would be considered class 2-B... possible carcinogin

EXAM-017-003 Swerdlow is the Chairperson of the AGNIR 2003 report...the AGNIR is a branch of NRPB, the technical and not health group, which develops guidelines in the UK, similar to the FCC guidelines but was also supposed to monitor scientific research on health effects from EMF.

Because the AGNIR/NRPB did not do it's job properly, in 1999 the UK Minister for Public Health announced the formation of a temporary Independent Expert Group on Mobile Phones (IEGMP) headed by Professor Stewart to review the health effects of EMF from mobile phones. The IEGMP produced a review of the current state of EMF research (Stewart Report) and devoted an entire section to the NRPB's past role in EMF research which roundly critcized AGNIR/NRPB for not doing it's job (see excerpt below and attached doc's regarding same) and said it was not serving the public health interest.

IEGMP suggested that the AGNIR review the EMF research every 3 years.....AGNIR produced a report in 2003 and then waited nine (9) years to produce another report in 2012 which by this time with a couple of 2011 exceptions featured data only as recent as 2010.

Professor Swerdlow, the head of the AGNIR group has also been critized for industry ties (if you want the ref for Swerdlow..let me know and I will dig it out.

See Stewart Report [attached] sections: 3.35-3.47 and 1.66 for criticisms of AGNIR

3.42 In general, we believe that NRPB has [redacted]

EXM-017-004; what has Carpenter said in the past about this? He should definitely say other devices are not the subject of this case and that due to the Gaps in knowledge on how non-thermal and thermal RF effects children short and long term ....all RF should be halted.

-----Original Message-----
From: CQMAdministrator <CQMAdministrator@maine.gov>
To: dnwilkins <dnwilkins@aol.com>
Sent: Tue, Mar 12, 2013 3:18 pm
Subject: A DR set of ID EXM-017 has been submitted for case no 2011-00262

DR Set of ID NO (EXM-017) has been generated regarding Case Number 2011-00262 for your attention.
Please provide your response to the question(s) shown below.

DR Question ID	Question Description	Question Text
EXM-017-001	Examiners' Supplemental Data Requests (Carpenter)	Regarding your testimony on page 17 "In the context of exposure to RF emissions from smart meters, there is a substantial body of evidence from the personal accounts of utility customers who report experiencing EHS symptoms," please discuss whether there is anything different about the nature smart meter RF emissions that would make it more likely to cause EHS symptoms than RF emissions from other devices such as cell phone and wireless computer routers. Please also discuss whether you are aware EHS sensitivity symptoms that might be caused by other RF emitting devices.
EXM-017-002	Examiners' Supplemental Data Requests (Carpenter)	On page 22 of your testimony, you state that "[t]he weight of evidence indicates that mobile phone use is associated with elevated risk of brain cancer?." Please discuss whether it is also you opinion that the weight of the evidence indicates that the use of smart meters by utilities is associated with an elevated risk of brain cancer or other forms of cancer.
EXM-017-003	Examiners' Supplemental Data Requests (Carpenter)	Regarding your testimony on page 23, please discuss reasons why the UK Advisory Group on Non-Ionizing Radiation would publish a biased report.
EXM-017-004	Examiners' Supplemental Data Requests (Carpenter)	Regarding your testimony on page 29 "In the meantime it is extremely unwise to implement the smart grid with wireless smart meters until we understand fully the potential for harm to human health," (a) please discuss your view as to whether wireless smart meter deployment should be prohibited pending further study, assuming that customers can choose not to have a smart meter installed on their premise and would not be required to place RF devices on their appliance to communicate with the smart meter; and (b) please discuss your view as to whether other RF emission devices should not be deployed

CARPENTER DEPO
EXHIBIT 22

Ed Freedm

Smart meters — opt out
Disability clause

Have to pay fee monthly

So shouldn't have to pay
for something you don't have
under Am Disability Act

Illegal surcharges

Defense says no link between
Smart meter & Ed's cancer
Waldenstrom non Hodgkins
Hodgkin Bone Jt pain

Ed must prove that having a
Smart meter actually result
worsening his symptom &
cancer progression.

RDS

Written report due Nov 1

Report would be about
impact of [illegible] [illegible]
would ↑ risk of symptoms
of non-Hodgkin's

Does this ↑ of [illegible] [illegible]
symptoms

Use layman term re non-Hodgkin
Waldenström is rare
[illegible]

Designated 2013

↑ IgM levels